BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 295/20, 211/26, 233/14, A61K 31/495 — A1

(11) International Publication Number: WO 98/04537

(43) International Publication Date: 5 February 1998 (05.02.98)

(21) International Application Number: PCT/US97/13422

(22) International Filing Date: 30 July 1997 (30.07.97)

(30) Priority Data:

60/023,139	30 July 1996 (30.07.96)	US
08/895,772	17 July 1997 (17.07.97)	US

(71) Applicant *(for all designated States except US)*: ARRIS PHARMACEUTICAL CORPORATION [US/US]; 180 Kimball Way, South San Francisco, CA 94080 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: DENER, Jeffrey, Mark [US/US]; 850 Campus Drive #106, Daly City, CA 94015 (US). KUO, Elaine, Yee-Lin [US/US]; 1814 Arch Street, Berkeley, CA 94709 (US). RICE, Ken, Duane [US/US]; 7 Tomales Street, Sausalito, CA 94965 (US). WANG, Vivian, Rueywen [US/US]; 530 Shannon Way #4215, Redwood City, CA 94065 (US). YOUNG, Wendy, Beth [US/US]; 1919 The Alameda #21, San Mateo, CA 94403 (US).

(74) Agents: DOW, Karen, B. et al.; Townsend and Townsend and Crew LLP, 8th floor, Two Embarcadero Center, San Francisco, CA 94111-3834 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: NOVEL COMPOUNDS AND COMPOSITIONS FOR TREATING DISEASES ASSOCIATED WITH TRYPTASE ACTIVITY

(57) Abstract

The present invention relates to novel compounds which are typtase inhibitors; the pharmaceutically acceptable salts and *N*-oxides thereof; their uses as therapeutic agents and the methods of their making.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Paso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

NOVEL COMPOUNDS AND COMPOSITIONS FOR TREATING DISEASES ASSOCIATED WITH TRYPTASE ACTIVITY

This application claims the benefit of U.S. Provisional Application No. 60/023,139, filed July 30, 1996.

Field of the Invention:

This invention relates to novel methods and compositions for treating diseases associated with tryptase activity by administration of novel tryptase inhibitors.

Description of the Field:

Tryptase, the predominant protease secreted from human mast cells, is thought to be involved in neuropeptide processing and tissue inflammation. Tryptase concentrations are elevated in the bloodstream for several hours following anaphylaxis (Schwartz *et al.* (1987) *N. Eng. J. Med.* 316:1622-1626), are increased in nasal and lung lavage fluid from atopic subjects following specific antigen challenge (Castells *et al.* (1988) *J. Allerg. Clin. Immunol.* 141:563-568) and are elevated in lung lavage fluid of atopic asthmatics after endobronchial allergen challenge. Smokers often have striking elevations of bronchoalveolar lavage fluid tryptase levels, a finding that provides some support for the hypothesis that release of proteinase from activated mast cells could contribute to lung destruction in smoker's emphysema. (Celenteron *et al.* (1988) *Chest* 94:119-123). In addition, tryptase has been shown to be a potent mitogen for fibroblasts, suggesting that it is involved in pulmonary fibrosis and interstitial lung disease (Ross *et al.* (1991) *J. Clin. Invest.* 88:493-499).

Asthma is recognized as an inflammatory disorder (Hood *et al.* (1984) In: Benjamin-Cummings, ed. *Immunology* 2nd ed.) and frequently is characterized by progressive development of hyper responsiveness of the trachea and bronchi to both immunospecific allergens and generalized chemical or physical stimuli. The disease involves multiple biochemical mediators in both its acute and chronic stages. The hyper responsiveness of asthmatic bronchiolar tissue is believed to be the result of chronic inflammatory reactions, which irritate and damage the epithelium lining the airway wall and promote pathological thickening of

the underlying tissue. Bronchial biopsies in patients with only mild asthma have features of inflammation in the airway wall.

Allergic responses to inhaled allergens can initiate the inflammatory sequence. For example, allergens can activate mast cells and basophils, which are present in the epithelium and underlying smooth muscle tissue by binding IgE located on the cell surface. Activated mast cells release a number of preformed or primary chemical mediators (e.g., histamine) of the inflammatory response and generate numerous other secondary mediators of inflammation (e.g., superoxide, lipid derived mediators, etc.) *in situ*. In addition, several large molecules (e.g., proteoglycans, tryptase, chymase, etc.) are released by degranulation of mast cells.

The release of these preformed mediators from mast cells probably accounts for the early bronchiolar constriction in the asthmatic reaction to air borne allergens. The early phase of the asthmatic reaction peaks approximately fifteen minutes after exposure to allergen and is generally followed by recovery over the ensuing one to two hours. Twenty five to thirty five percent of the patient population experience a further decline in respiratory function which maximizes six to twelve hours after exposure. This late reaction phase is accompanied by a marked increase in the number of inflammatory cells (e.g., eosinophils, neutrophils, lymphocytes, etc.) infiltrating the bronchiolar tissue. The infiltrating cells are attracted to the site by release of mast cell derived chemotactic agents and then become activated during the late reaction phase. The late asthmatic response is believed to be a secondary inflammatory reaction mediated in part by the secretory activity of granulocytes.

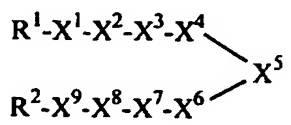
Tryptase is implicated in the degradation of vasodilating and bronchorelaxing neuropeptides (Caughey *et al.* (1988) *J.Pharmacol. Exp. Ther.* 244:133-137; Franconi *et al.* (1988) *J. Pharmacol. Exp. Ther.* 248:947-951; and Tam *et al.* (1990) *Am. J. Respir. Cell Mol. Biol.* 3:27-32) and modulation of bronchial responsiveness to histamine (Sekizawa *et al.* (1989) *J. Clin. Invest.* 83:175-179). These findings suggest that tryptase may increase bronchoconstriction in asthma by destroying bronchodilating peptides. Tryptase cleaves fibrinogen α-chains and high molecular weight kinninogen, which suggests that tryptase plays a role with heparin as a local anticoagulant. Tryptase activates prostromelysin (pro-MMP-3) and procollagenase (pro-MMP-1) via MMP-3, which suggests that tryptase is involved in tissue inflammation and remodeling and joint destruction in rheumatoid arthritis. Further,

administration of tryptase inhibitor protects against development of the late and airway hyper responsive phases in allergen challenged sheep (Clark *et al.* (1995) *Am. J. Respir. Crit. Care Med.* 152: 2076-2083) and inhibits the immediate cutaneous response to intradermal injection of allergen in allergic sheep (Molinari *et al.* (1995) *Amer. Physiol. Soc.* 79(6):1966-1970). All of the above-described findings clearly indicate the applicability of tryptase inhibitors as therapeutic agents in treating asthma and other disorders associated with inflammation of the respiratory tract.

The disclosures of these and other documents referred to throughout this application are incorporated herein by reference.

SUMMARY OF THE INVENTION

This application relates to a compound of Formula I:



I

in which:

X^5 is (C_{3-14})cycloalkylene, hetero(C_{3-14})cycloalkylene, (C_{6-14})arylene or hetero(C_{5-14})arylene;

X^4 and X^6 are independently (C_{0-2})alkylene;

X^1 and X^9 are independently a covalent bond, -C(O)-, -C(O)O-, -OC(O)-, -C(O)N(R^3)-, -N(R^3)C(O)-, -S(O)$_2$N(R^3)-, -N(R^3)S(O)$_2$-, -OC(O)N(R^3)-, -N(R^3)C(O)O-, -N(R^3)C(O)N(R^3)- or -OC(O)O-, wherein each R^3 is independently hydrogen, (C_{1-3})alkyl or (C_{3-8})cycloalkyl, with the proviso that X^1 and X^9 are not both covalent bonds;

X^3 and X^7 are independently -C(O)-, -C(O)O-, -OC(O)-, -C(O)N(R^3)-, -N(R^3)C(O)-, -S(O)$_2$N(R^3)-, -N(R^3)S(O)$_2$-, -OC(O)N(R^3)-, -N(R^3)C(O)O-, -N(R^3)C(O)N(R^3)- or -OC(O)O-, wherein R^3 is as defined above;

X^2 and X^8 are independently (C_{1-8})alkylene, hetero(C_{1-8})alkylene, $-X^{10}-X^{11}-$ or $-X^{11}-X^{10}-$, wherein X^{10} is (C_{0-4})alkylene or hetero(C_{3-4})alkylene and X^{11} is (C_{3-8})cycloalkylene or hetero(C_{3-8})cycloalkylene;

R^1 is $R^4-X^{12}-$ or $R^5-X^{13}-$, wherein:

R^4 is amino, amidino, guanidino, 1-iminoethyl or methylamino,

X^{12} is (C_{4-6})alkylene, hetero(C_{4-6})alkylene, heterooxo(C_{4-6})alkylene, oxo(C_{4-6})alkylene or $-X^{14}-X^{15}-X^{16}-$, wherein X^{15} is (C_{3-6})cycloalkylene, hetero(C_{5-6})arylene, hetero(C_{3-6})cycloalkylene or phenylene, X^{14} is (C_{n14})alkylene and X^{16} is (C_{n16})alkylene, wherein the sum of n14 and n16 is 0, 1, 2, 3 or 4,

R^5 is a group selected from azetidin-3-yl, benzoimidazol-4-yl, benzoimidazol-5-yl imidazol-1-yl, imidazol-2-yl, imidazol-4-yl, 2-imidazolin-2-yl, 2-imidazolin-3-yl, 2-methylimidazol-1-yl, 4-methylimidazol-1-yl, 5-methylimidazol-1-yl, 1-methylpiperid-3-yl, 1-methylpiperid-4-yl, piperid-3-yl, piperid-4-yl, piperazin-1-yl, piperazin-2-yl, pyrid-3-yl, pyrid-4-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrrolidin-3-yl, 1,4,5,6-tetrahydropyrimidin-2-yl, 1,4,5,6-tetrahydropyrimidin-4-yl and 1,4,5,6-tetrahydropyrimidin-5-yl and any carbocyclic ketone or thioketone derivative thereof, which group is optionally substituted with one or more radicals selected from halo, hydroxy, mercapto, (C_{1-8})alkyl, (C_{3-14})cycloalkyl, (C_{6-14})aryl, (C_{6-14})aryl(C_{1-4})alkyl, (C_{1-8})alkanoyl, (C_{1-8})alkyloxy, (C_{6-14})aryloxy, (C_{3-14})cycloalkyloxy, (C_{1-4})alkyloxy, (C_{1-8})alkylthio, (C_{3-14})cycloalkylthio, (C_{6-14})arylthio and $-NR^6R^7$, wherein R^6 and R^7 are independently selected from hydrogen, (C_{1-8})alkyl, (C_{1-8})alkanoyl, (C_{3-14})cycloalkyl or (C_{6-14})aryl and

X^{13} is (C_{0-6})alkylene, hetero(C_{2-6})alkylene, heterooxo(C_{3-6})alkylene, oxo(C_{2-6})alkylene or $-X^{17}-X^{18}-X^{19}-$, wherein X^{18} is as defined above for X^{15}, X^{17} is (C_{n17})alkylene and X^{18} is (C_{n18})alkylene, wherein the sum of n17 and n18 is 0, 1 or 2; and

R^2 is $R^8-X^{20}-$ or $R^9-X^{21}-$, wherein:

R^8 is amino, 1-iminoethyl or methylamino,

X^{20} is (C_{4-6})alkylene, hetero(C_{4-6})alkylene, heterooxo(C_{4-6})alkylene, oxo(C_{4-6})alkylene or $-X^{22}-X^{23}-X^{24}-$, wherein X^{23} is as defined above for X^{15}, X^{22} is (C_{n22})alkylene and X^{24} is (C_{n24})alkylene, wherein the sum of n22 and n24 is 0, 1, 2, 3 or 4,

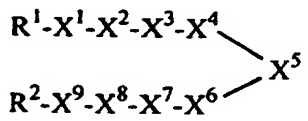
with the proviso that when R^8 is amino then X^{22} is not (C_{4-6})alkylene or oxa(C_{4-6})alkylene and n22 is not 1, 2, 3 or 4,

R^9 is as defined above for R^5 and

X^{21} is (C_{0-6})alkylene, hetero(C_{2-6})alkylene, heterooxo(C_{3-6})alkylene, oxo(C_{2-6})alkylene or $-X^{25}-X^{26}-X^{27}-$, wherein X^{26} is as defined above for X^{15}, X^{25} is (C_{n25})alkylene and X^{27} is (C_{n27})alkylene, wherein the sum of n25 and n27 is 0, 1 or 2; wherein each alkylene, cycloalkylene, heteroalkylene, heterocycloalkylene, phenylene, arylene and heteroarylene, as defined above, are optionally substituted with one or more radicals selected from halo, hydroxy, mercapto, (C_{1-8})alkyl, (C_{3-14})cycloalkyl, (C_{6-14})aryl, (C_{6-14})aryl(C_{1-4})alkyl, (C_{1-8})alkanoyl, (C_{1-8})alkyloxy, (C_{6-14})aryloxy, (C_{3-14})cycloalkyloxy, (C_{1-4})alkyloxy, (C_{1-8})alkylthio, (C_{3-14})cycloalkylthio, (C_{6-14})arylthio and $-NR^6R^7$, wherein R^6 and R^7 are as defined above; with the proviso that covalent bonds do not occur between heteroatoms contained within R^1, X^2, X^4, X^6, X^8 and R^2 and any heteroatoms contained with X^3, X^5, X^7 and X^9; and

the pharmaceutically acceptable salts, *N*-oxides, prodrug derivatives and protected derivatives thereof.

A second aspect of this application relates to a compound of Formula I:



I

in which:

X^4-X^5-X^6 together are (C_{2-12})alkylene or hetero(C_{3-12})alkylene;

X^1 and X^9 are independently a covalent bond, -C(O)-, -C(O)O-, -OC(O)-, -C(O)N(R^3)-, -N(R^3)C(O)-, -S(O)$_2$N(R^3)-, -N(R^3)S(O)$_2$-, -OC(O)N(R^3)-, -N(R^3)C(O)O-, -N(R^3)C(O)N(R^3)- or -OC(O)O-, wherein each R^3 is independently hydrogen, (C_{1-3})alkyl or (C_{3-8})cycloalkyl, with the proviso that X^1 and X^9 are not both covalent bonds;

X^3 and X^7 are independently -C(O)-, -C(O)O-, -OC(O)-, -C(O)N(R^3)-, -N(R^3)C(O)-,

$-S(O)_2N(R^3)-$, $-N(R^3)S(O)_2-$, $-OC(O)N(R^3)-$, $-N(R^3)C(O)O-$, $-N(R^3)C(O)N(R^3)-$ or $-OC(O)O-$, wherein R^3 is as defined above;

X^2 and X^8 are independently (C_{1-8})alkylene, hetero(C_{1-8})alkylene, $-X^{10}-X^{11}-$ or $-X^{11}-X^{10}-$, wherein X^{10} is (C_{0-4})alkylene or hetero(C_{3-4})alkylene and X^{11} is (C_{3-8})cycloalkylene or hetero(C_{3-8})cycloalkylene;

R^1 is $R^4-X^{12}-$ or $R^5-X^{13}-$, wherein:

R^4 is amino, amidino, guanidino, 1-iminoethyl or methylamino,

X^{12} is (C_{4-6})alkylene, hetero(C_{4-6})alkylene, heterooxo(C_{4-6})alkylene, oxo(C_{4-6})alkylene or $-X^{14}-X^{15}-X^{16}-$, wherein X^{15} is (C_{3-6})cycloalkylene, hetero(C_{5-6})arylene, hetero(C_{3-6})cycloalkylene or phenylene, X^{14} is (C_{n14})alkylene and X^{16} is (C_{n16})alkylene, wherein the sum of n14 and n16 is 0, 1, 2, 3 or 4,

R^5 is a group selected from azetidin-3-yl, benzoimidazol-4-yl, benzoimidazol-5-yl imidazol-1-yl, imidazol-2-yl, imidazol-4-yl, 2-imidazolin-2-yl, 2-imidazolin-3-yl, 2-methylimidazol-1-yl, 4-methylimidazol-1-yl, 5-methylimidazol-1-yl, 1-methylpiperid-3-yl, 1-methylpiperid-4-yl, piperid-3-yl, piperid-4-yl, piperazin-1-yl, piperazin-2-yl, pyrid-3-yl, pyrid-4-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrrolidin-3-yl, 1,4,5,6-tetrahydropyrimidin-2-yl, 1,4,5,6-tetrahydropyrimidin-4-yl and 1,4,5,6-tetrahydropyrimidin-5-yl and any carbocyclic ketone or thioketone derivative thereof, which group is optionally substituted with one or more radicals selected from halo, hydroxy, mercapto, (C_{1-8})alkyl, (C_{3-14})cycloalkyl, (C_{6-14})aryl, (C_{6-14})aryl(C_{1-4})alkyl, (C_{1-8})alkanoyl, (C_{1-8})alkyloxy, (C_{6-14})aryloxy, (C_{3-14})cycloalkyloxy, (C_{1-4})alkyloxy, (C_{1-8})alkylthio, (C_{3-14})cycloalkylthio, (C_{6-14})arylthio and $-NR^6R^7$, wherein R^6 and R^7 are independently selected from hydrogen, (C_{1-8})alkyl, (C_{1-8})alkanoyl, (C_{3-14})cycloalkyl or (C_{6-14})aryl and

X^{13} is (C_{0-6})alkylene, hetero(C_{2-6})alkylene, heterooxo(C_{3-6})alkylene, oxo(C_{2-6})alkylene or $-X^{17}-X^{18}-X^{19}-$, wherein X^{18} is as defined above for X^{15}, X^{17} is (C_{n17})alkylene and X^{18} is (C_{n18})alkylene, wherein the sum of n17 and n18 is 0, 1 or 2; and

R^2 is $R^8-X^{20}-$ or $R^9-X^{21}-$, wherein:

R^8 is as defined above for R^4,

X^{20} is (C_{4-6})alkylene, hetero(C_{4-6})alkylene, heterooxo(C_{4-6})alkylene,

oxo(C_{4-6})alkylene or -X^{22}-X^{23}-X^{24}-, wherein X^{23} is as defined above for X^{15}, X^{22} is (C_{n22})alkylene and X^{24} is (C_{n24})alkylene, wherein the sum of n22 and n24 is 0, 1, 2, 3 or 4,

R^9 is as defined above for R^5 and

X^{21} is (C_{0-6})alkylene, hetero(C_{2-6})alkylene, heterooxo(C_{3-6})alkylene, oxo(C_{2-6})alkylene or -X^{25}-X^{26}-X^{27}-, wherein X^{26} is as defined above for X^{15}, X^{25} is (C_{n25})alkylene and X^{27} is (C_{n27})alkylene, wherein the sum of n25 and n27 is 0, 1 or 2;

wherein each alkylene, cycloalkylene, heteroalkylene, heterocycloalkylene, phenylene, arylene and heteroarylene, as defined above, are optionally substituted with one or more radicals selected from halo, hydroxy, mercapto, (C_{1-8})alkyl, (C_{3-14})cycloalkyl, (C_{6-14})aryl, (C_{6-14})aryl(C_{1-4})alkyl, (C_{1-8})alkanoyl, (C_{1-8})alkyloxy, (C_{6-14})aryloxy, (C_{3-14})cycloalkyloxy, (C_{1-4})alkyloxy, (C_{1-8})alkylthio, (C_{3-14})cycloalkylthio, (C_{6-14})arylthio and -NR^6R^7, wherein R^6 and R^7 are as defined above; with the proviso that covalent bonds do not occur between heteroatoms contained within R^1, X^2, X^4, X^6, X^8 and R^2 and any heteroatoms contained with X^3, X^5, X^7 and X^9; and

the pharmaceutically acceptable salts, *N*-oxides, prodrug derivatives and protected derivatives thereof.

A third aspect of this invention is a pharmaceutical composition which contains a compound of Formula I, or a pharmaceutically acceptable salt, *N*-oxide or prodrug derivative thereof in admixture with one or more suitable excipients.

A fourth aspect of this invention is a method of treating a disease in an animal in which tryptase activity contributes to the pathology and/or symptomatology of the disease, which method comprises administering to the animal a therapeutically effective amount of compound of Formula I or a pharmaceutically acceptable salt, *N*-oxide or prodrug derivative thereof.

A fifth aspect of this invention is the processes for preparing compounds of Formula I and the pharmaceutically acceptable salts, *N*-oxides, prodrug derivatives and protected derivatives thereof as set forth in "Detailed Description of the Invention".

DETAILED DESCRIPTION OF THE INVENTION

Definitions:

Unless otherwise stated, the following terms used in the specification and claims have the meanings given below:

"Alkanoyl" means the radical -C(O)R, wherein R is alkyl as defined below, having overall the number of carbon atoms indicated (e.g., (C_{1-8})alkanoyl includes the radicals formyl, acetyl, propionyl, butyryl, isobutyryl, crotonoyl, isocrotonyl, etc.).

"Alkyl", as in alkyl, arylalkyl, alkyloxy, alkylthio, means a straight or branched, saturated or unsaturated hydrocarbon radical having the number of carbon atoms indicated (e.g., (C_{1-8})alkyl includes methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, isobutyl, *tert*-butyl, vinyl, allyl, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methylallyl, ethynyl, 1-propynyl, 2-propynyl, etc.).

"Alkylene" means a straight, saturated or unsaturated hydrocarbon divalent radical having the number of carbon atoms indicated (e.g., (C_{0-6})alkylene includes methylene (-CH_2-), ethylene (-$(CH_2)_2$-), vinylene (-CH:CH-), ethynylene (-C ⋮ C-), 2-propylene (-CH:CH·CH_2-), 1-propylene (-CH_2·CH:CH-), tetramethylene (-$(CH_2)_4$-), pentamethylene (-$(CH_2)_5$-) and hexamethylene (-$(CH_2)_6$-), etc.). The term (C_0)alkylene is meant to represent a covalent bond.

"Alkyloxy" means the radical -OR, wherein R is alkyl as defined above, having the number of carbon atoms indicated (e.g., (C_{1-8})alkyloxy includes the radicals methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, etc.).

"Alkylthio" means the radical -SR, wherein R is alkyl as defined above, having the number of carbon atoms indicated (e.g., (C_{1-8})alkylthio includes the radicals methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, etc.).

"Animal" includes humans, non-human mammals (e.g., dogs, cats, rabbits, cattle, horses, sheep, goats, swine, deer, etc.) and non-mammals (e.g., birds, etc.).

"Aryl", as in aryl, arylalkyl, aryloxy and arylthio, means an aromatic monocyclic or polycyclic hydrocarbon radical containing the number of carbon atoms indicated, wherein the carbon atom with the free valence is a member of an aromatic ring, and any carbocylic ketone or thioketone derivative thereof (e.g., (C_{6-14})aryl includes phenyl, naphthyl, anthracenyl, phenanthrenyl, 1,2,3,4-tetrahydronaphth-5-yl, 1-oxo-1,2-dihydronaphth-6-yl, 1-thioxo-1,2-dihydronaphth-7-yl, etc.).

"Arylene" means an aromatic monocyclic or polycyclic hydrocarbon divalent radical

containing the number of carbon atoms indicated, wherein the carbon atoms with the free valence are members of an aromatic ring, and any carbocylic ketone or thioketone derivative thereof (e.g., (C_{6-14})arylene includes 1,4-phenylene, 1,3-phenylene, 1,4-naphthylene, 2,6-naphthylene, 1,4-anthracenylene, 2,6-anthracenylene, 1,6-phenanthrenylene, 1,2,3,4-tetrahydro-5,8-naphthylene, 1-oxo-1,2-dihydro-5,7-naphthylene, 1-thioxo-1,2-dihydro-5,8-naphthylene, etc.).

"Aryloxy" means the radical -OR, wherein R is aryl, as defined above, having the number of carbon atoms indicated (e.g., (C_{6-14})aryloxy includes the radicals phenoxy, naphthyloxy, anthracenyloxy, etc.).

"Arylthio" means the radical -SR, wherein R is aryl, as defined above, having the number of carbon atoms indicated (e.g., (C_{6-14})arylthio includes the radicals phenylthio, naphthylthio, anthracenylthio, etc.).

"Cycloalkyl", as in cycloalkyl and cycloalkyloxy, means a saturated or unsaturated, monocyclic or polycyclic hydrocarbon radical containing the number of carbon atoms indicated, wherein the carbon atom with the free valence is a member of a non-aromatic ring, and any carbocyclic ketone and thioketone derivative thereof (e.g., (C_{3-14})cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, 2,5-cyclohexadienyl, bicyclo[2.2.2]octyl, 1,2,3,4-tetrahydronaphth-1-yl, oxocyclohexyl, dioxocyclohexyl, thiocyclohexyl, etc.).

"Cycloalkylene" means a saturated or unsaturated, monocyclic or polycyclic hydrocarbon divalent radical containing the number of carbon atoms indicated, wherein the carbon atoms with the free valence are members of a non-aromatic ring, and any carbocyclic ketone and thioketone derivative thereof (e.g., (C_{3-6})cycloalkylene includes 1,2-cyclopropylene, 1,2-cyclobutylene, 1,3-cyclobutylene, 1,2-cyclopentylene, 1,3-cyclopentylene, 1,4-cyclopentylene, 1,4-cyclohexylene, 3-cyclohexen-1,2-ylene, 2,5-cyclohexadien-1,4-ylene, 1,4-bicyclo[2.2.2]octylene, 1,2,3,4-tetrahydro-1,4-naphthylene, 5-oxo-1,3-cyclohexylene, 2,5-dioxo-1,4-cyclohexylene, 5-thioxo-1,4-cyclohexylene, etc.).

"Cycloalkyloxy" means the radical -OR, wherein R is cycloalkyl, as defined above, having the number of carbon atoms indicated (e.g., (C_{3-14})cycloalkyloxy includes the radicals cyclopropoxy, cyclobutoxy, cyclopentyloxy, cyclohexyloxy, etc.).

"Cycloalkylthio" means the radical -OR, wherein R is cycloalkyl, as defined above, having the number of carbon atoms indicated (e.g., (C_{3-14})cycloalkylthio includes the radicals cyclopropylthio, cyclobutylthio, cyclopentylthio, cyclohexylthio, etc.).

"Deprotecting" refers to removing any protective groups present after the selective reaction has been carried out.

"Disease" specifically includes any unhealthy condition of an animal or part thereof and includes an unhealthy condition which may be caused by, or incident to, medical or veterinary therapy applied to that animal, i.e., the "side effects" of such therapy.

"Halo" means fluoro, chloro, bromo or iodo.

"Heteroalkylene" means alkylene, as defined above, wherein 1 to 5 of the carbon atoms indicated is replaced by a heteroatom chosen from N, O or S (e.g., azaalkylene, oxaalkylene and thiaalkylene, respectively), with the proviso that the oxygen, nitrogen and sulfur atoms contained therein do not form bonds with other heteroatoms. For example, hetero(C_{3-12})alkylene is meant to encompass aza(C_3)alkylene which includes 3-azatrimethylene (-$NHCH_2CH_2$-), 2-azatrimethylene (-CH_2·NH·CH_2-), etc.; ω-aza(C_{2-5})alkylene which includes 2-azaethylene (-NH·CH_2-), 3-azatrimethylene, 4-azatetramethylene (-NH·CH_2·CH_2·CH_2-) and 5-azapentamethylene (-NH·CH_2·CH_2·CH_2·CH_2-); oxa(C_3)alkylene which includes as 3-oxatrimethylene (-O·CH_2·CH_2-), 2-oxatrimethylene (-CH_2·O·CH_2-), etc.; oxa(C_5)alkylene such as 3-oxapentamethylene (-CH_2·CH_2·O·CH_2·CH_2-), etc.; thia(C_3)alkylene which includes 3-thiatrimethylene (-S·CH_2·CH_2-), 2-thiatrimethylene (-CH_2·S·CH_2-), etc.; ω-thia(C_{2-4})alkylene which includes 2-thiaethylene (-NH·CH_2-), 3-thiatrimethylene and 4-thiatetramethylene (-S·CH_2·CH_2·CH_2-); diaza(C_6)alkylene which includes 2,5-diazahexamethylene (-CH_2·NH·CH_2·CH_2·NH·CH_2-); azaoxa(C_6)alkylene which includes 2,-oxa-5-azahexamethylene (-CH_2·O·CH_2·CH_2·NH·CH_2-); and the like.

"Heteroarylene" means arylene, as defined above, wherein 1 to 5 of the carbon atoms indicated are replaced by a heteroatom chosen from N, O or S (e.g., hetero(C_{5-6})arylene includes furylene, thienylene, pyrrolylene, imidazolylene, pyridylene, etc.).

"Heterocycloalkylene" means cycloalkylene, as defined above, wherein 1 to 5 of the carbon atoms indicated are replaced by a heteroatom chosen from N, O, or S (e.g., hetero(C_{3-14})cycloalkylene includes 2,4-pyrrolidinylene, 2,4-pyrrolinylene,

2,4-imidazolinylene, 2,4-imidazolinylene, 3,5-pyrazolinylene, 1,4-piperidylene, 1,4-piperazinylene, 2,5-quinuclidinylene, 2,5-morpholinylene, 1.3-isoindolinylene, etc.).

"Heterooxoalkylene" means alkylene, as defined above, wherein one of the number of carbon atoms indicated is replaced by a heteroatom chosen from N, O or S and a carbon atom adjacent to the heteroatom is replaced by a carbonyl group (C=O), e.g., azaoxoalkylene, oxaoxoalkylene and thiaoxoalkylene, respectively, with the proviso that the oxygen, nitrogen and sulfur atoms contained therein do not form bonds with other heteroatoms. For example, heterooxo(C_{4-6})alkylene is meant to encompass azaoxo(C_3)alkylene which includes 2-aza-3-oxotrimethylene (-C(O)·NH·CH_2-), 3-aza-2-oxotrimethylene (-NH·C(O)·CH_2-), etc.; oxaoxo(C_3)alkylene which includes 2-oxa-3-oxotrimethylene (-C(O)·O·CH_2-), 3-oxa-2-oxotrimethylene (-O·C(O)·CH_2-), etc.; and thiaoxo(C_3)alkylene which includes 2-thia-3-oxotrimethylene (-C·(O)·S·CH_2-), 3-thia-2-oxotrimethylene (-S·C(O)·CH_2-), etc.

"Leaving group" has the meaning conventionally associated with it in synthetic organic chemistry, i.e., an atom or group displaceable under alkylating conditions, and includes, halogen, hydroxy, alkylsulfonloxy (e.g., mesyloxy, ethanesulfonyloxy, etc.), arylsulfonyloxy (e.g., benzenesulfonyloxy and tosyloxy, thienyloxy), dihalophosphinoyloxy, tetrahalophosphaoxy, and the like.

"Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, the phrase "optionally substituted with one or more radicals" means that the group referred to may or may not be substituted in order to fall within the scope of the invention.

"Pharmaceutically acceptable *N*-Oxide" means compound in which nitrogens are in an oxidized state (i.e., O←N) which are pharmaceutically acceptable, as defined below, and which possess the desired pharmacological activity. The *N*-oxides of compounds of Formula I can be prepared by methods known to those of ordinary skill in the art.

"Oxoalkylene" means alkylene, as defined above, wherein one of the number of carbon atoms indicated is replaced by a carbonyl group (C=O), e.g., oxo(C_3)alkylene includes 3-oxotrimethylene (-C(O)·CH_2·CH_2-), etc..

"Pathology" of a disease means the essential nature, causes and development of the

disease as well as the structural and functional changes that result from the disease processes.

"Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

"Pharmaceutically acceptable salts" means salts which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids such as hydrobromic acid, hydrochloric acid, nitric acid, phosphoric acid, sulfuric acid and the like; or with organic acids such as acetic acid, benzenesulfonic acid, benzoic acid, camphorsulfonic acid, *p*-chlorobenzene-sulfonic acid, cinnamic acid, citric acid, cyclopentanepropionic acid, 1,2-ethanedisulfonic acid, ethanesulfonic acid, fumaric acid, glucoheptonic acid, gluconic acid, glutamic acid, glycolic acid, hexanoic acid, heptanoic acid, *o*-(4-hydroxybenzoyl)benzoic acid, 2-hydroxyethanesulfonic acid, hydroxynaphthoic acid, lactic acid, lauryl sulfuric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), muconic acid, 2-naphthalenesulfonic acid, oxalic acid, 3-phenylpropionic acid, propionic acid, pyruvic acid, salicylic acid, stearic acid, succinic acid, tartaric acid, tertiary butylacetic acid, *p*-toluenesulfonic acid, trimethylacetic acid and the like.

Pharmaceutically acceptable salts also include base addition salts which may be formed when acidic protons present are capable of reacting with inorganic or organic bases. Acceptable inorganic bases include aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate and sodium hydroxide. Acceptable organic bases include diethanolamine, ethanolamine, *N*-methylglucamine, triethanolamine, tromethamine and the like.

"Phenylene" means the divalent aromatic radical $-C_6H_4-$ and includes 1,4-phenylene, 1,3-phenylene and the like.

"Pharmaceutically acceptable prodrug derivatives" means derivatives of compounds of Formula I which are pharmaceutically acceptable, as defined above, and which are converted *in vivo* to the corresponding non-derivatized form of a compound of Formula I. Such prodrugs include compounds of Formula I which have *N*-acylated piperidyl (i.e., $N(P)C_5H_9-$), *N*-acylated azaalkylene (e.g., $-N(P)\cdot CH_2\cdot CH_2-$), *N*-acylated amino (i.e., $-NH_2(P)$), *N*-acylated amidino

(i.e.,-C(NP)·NHP, -C(NH)·NHP or -C(NP)·NH_2), *N*-acylated guanidino (i.e., -NHC(NP)·NHP, -NH·C(NH)·NHP or -NH·C(NP)·NH_2) groups, in which P is a group selected from -C(O)R^{10}, wherein R^{10} can be (C_{1-10})alkyloxy or *cis*-2-(C_{1-10})alkanoyloxyphenylvinyl, 3-(C_{1-10})alkanoyloxybutyryl, R^{11}-X^{28}-, wherein R^{11} is carboxy and X^{28} is (C_{1-10})alkylene or -C(O)·O·CH(R^{12})·O·C(O)R^{13}, wherein R^{12} is hydrogen, (C_{1-10})alkyl or (C_{3-10})cycloalkyl and R^{13} is (C_{1-10})alkyl.

"Protective group" has the meaning conventionally associated with it in synthetic organic chemistry, i.e., a group which selectively blocks one reactive site in a multifunctional compound such that a chemical reaction can be carried out selectively at another unprotected reactive site and which can be readily removed after the selective reaction is completed.

"Protecting agent" means an agent which will react with a multifunctional compound and create a protective group at a reactive site.

"Protected derivatives" in reference to a compound or a group means a derivative of compound or group in which a reactive site or sites are blocked with protective groups. Protected derivatives of compounds of Formula I are in themselves active as tryptase inhibitors and are useful in the preparation of other compounds of Formula I. Suitable protecting groups for reactive nitrogen atoms include *tert*-butoxycarbonyl, benzyloxycarbonyl and any other suitable amino protective groups (e.g., see T.W. Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc. 1981).

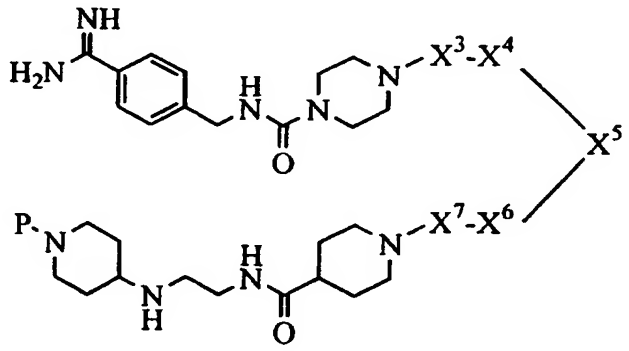
"Symptomatology" of a disease means any morbid phenomenon or departure from the normal in structure, function or sensation experienced by the patient and indicative of the disease, their production and the indications they furnish.

"Therapeutically effective amount" means that amount which, when administered to an animal for treating a disease, is sufficient to effect such treatment for the disease.

"Treating" or "treatment" of a disease includes preventing the disease from occurring in an animal which may be predisposed to the disease but does not yet experience or display symptoms of the disease, inhibiting the disease (i.e., arresting its development) or relieving the disease (i.e., causing regression of the disease).

The term "q.s." means adding a quantity sufficient to achieve a stated function, e.g., to bring a solution to the desired volume (i.e., 100%).

The compounds of Formula I and the intermediates and starting materials used in their preparation are named in accordance IUPAC rules of nomenclature in which the characteristic groups have decreasing priority for citation as the principle group as follows: acids, esters, amides and amidines. Furthermore, for the purposes of this Application, when referring to a divalent radical by written description the order of the number prefixes signifies the orientation of its attachment. Similarly, when referring to a divalent radical by formula the way in which the formula is presented signifies the orientation of attachment. For example, a compound of Formula I in which R^1 is 4-amidinobenzyl, X^1 and X^9 each are -NHC(O)-, X^2 is 1,4-piperazinylene, X^7 is -C(O)O-, X^8 is 4,1-piperidylene and R^2 is R^9-X^{21}, whercin R^9 is piperid-4-yl and X^{21} is 3-azatrimethylene, is illustrated by the following formula:



which compound is named:

cis-1,5-cyclooctylene 4-(4-amidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-(2-piperid-4-ylaminoethylcarbamoyl)-1-piperidinecarboxylate when X^3 and X^7 each are -C(O)O-, X^4 and X^6 each are a covalent bond, X^5 is *cis*-1,5-cyclooctylene and P is hydrogen;

3-{4-[2-(1-{*cis*-5-[4-(4-amidinobenzylcarbamoyl)piperazin-1-ylcarbonyloxy]cyclooctyloxy-carbonyl}piperid-4-ylcarbonylamino)ethylamino]piperid-1-ylcarbonyl}propionic acid when X^3 and X^7 each are -C(O)O-, X^4 and X^6 each are a covalent bond, X^5 is *cis*-1,5-cyclooctylene and P is 3-carboxypropionyl;

4-[4-(4-amidinobenzylcarbamoyl)piperazin-1-ylcarbonyl]benzyl 4-(2-piperid-4-ylaminoethylcarbamoyl)-1-piperadinecarboxylate when X^3 is -C(O)-, X^7 is -C(O)O-, X^4 is a covalent bond, X^6 is methylene, X^5 is phenylene and P is hydrogen;

1,4-tetramethylene 4-amidinobenzylcarbamoyl-1-piperazinecarboxylate when X^3 and X^7 are each is -C(O)O- and X^4-X^5-X^6 is 1,4-tetramethylene (i.e., -CH_2·CH_2·CH_2·CH_2-); and

N-4-amidinobenzyl-4-{5-[4-(2-piperid-4-ylaminoethylcarbamoyl)piperid-1-ylcarbonyl]valeryl}-1-piperazinecarboxamide when X^3 and X^7 are each is -C(O)- and X^4-X^5-X^6 is 1,4-tetramethylene (i.e., -CH_2·CH_2·CH_2·CH_2-).

Presently Preferred Embodiments:

While the broadest definition of this invention is set forth in the Summary of the Invention, certain compounds of Formula I are preferred. For example, preferred compounds of Formula I are those in which X^5 is *cis*-1,5-cyclooctylene and X^4 and X^6 each are a covalent bond, X^4-X^5-X^6 together are (C_{4-8})alkylene or X^5 is 1,4-phenylene and X^4 and X^6 are (C_{0-1})ethylene; X^1 and X^9 are independently a covalent bond, -C(O)-, -NHC(O)-, -C(O)NH-, -N(CH_3)C(O)- or -$S(O)_2$NH-, with the proviso that X^1 and X^9 are not both covalent bonds; X^3 and X^7 are independently -C(O)- or -C(O)O-; X^2 and X^8 are independently -X^{10}-X^{11}-, wherein X^{10} is a covalent bond or methylene and X^{11} is 4,1-piperidylene or 1,4-piperazinylene; R^1 is R^4-X^{12}- or R^5-X^{13}-, wherein R^4 is amidino, guanidino or methylamino, X^{12} is -X^{14}-X^{15}-X^{16}-, wherein X^{15} is 1,4-phenylene or 1,4-piperidylene, X^{14} is (C_{n14})alkylene and X^{16} is (C_{n16})alkylene, wherein the sum of n14 and n16 is 0, 1 or 2, R^5 is piperid-4-yl and X^{13} is (C_{2-3})alkylene; and R^2 is R^8-X^{20}- or R^9-X^{21}-, wherein R^8 is amino, amidino, guanidino, methylamino or 1-iminoethyl, X^{20} is -X^{22}-X^{23}-X^{24}-, wherein X^{23} is *trans*-1,4-cyclohexylene, 1,4-phenylene, 4,1-pyridylene, 1,4-piperidylene, X^{22} is (C_{n22})alkylene and X^{24} is (C_{n24})alkylene, wherein the sum of n22 and n24 is 1 or 2, R^9 is benzoimidazol-5-yl, imidazol-1-yl, imidazol-4-yl, 2-imidazolin-2-yl, 4-methylimidazol-1-yl, 5-methylimidazol-1-yl, 1-methylpiperid-4-yl, piperid-4-yl, piperazin-1-yl, pyrid-3-yl, pyrid-4-yl, 1,4,5,6-tetrahydropyrimidin-5-yl or 1,4,5,6-tetrahydro-2-dioxopyrimidin-5-yl and X^{21} is (C_{1-6})alkylene, ω-aza(C_{2-5})alkylene, 3-oxotrimethylene, ω-thia(C_{2-4})alkylene, 3-oxo-2-azatrimethylene, 3-aza-2-oxotrimethylene or -X^{25}-X^{26}-X^{27}-, wherein X^{26} is 1,4-phenylene, X^{25} is (C_{n25})alkylene and X^{24} is (C_{n27})alkylene, wherein the sum of n25 and n27 is 0 or 1; and the pharmaceutically acceptable salts, *N*-oxides, prodrug derivatives and protected derivatives thereof.

More preferred compounds of Formula I are those in which X^5 is *cis*-1,5-cyclooctylene

and X^4 and X^6 each are a covalent bond or X^4-X^5-X^6 together are (C_{4-8})alkylene; X^1 and X^9 are independently a covalent bond -C(O)-, -NHC(O)-, -C(O)NH- or -$S(O)_2$NH-, with the proviso that X^1 and X^9 are not both covalent bonds; X^3 and X^7 are independently -C(O)- or -C(O)O-; X^2 and X^8 are independently -X^{10}-X^{11}-, wherein X^{10} is a covalent bond or methylene and X^{11} is 4,1-piperidylene or 1,4-piperazinylene; R^1 is R^4-X^{12}-, wherein R^4 is amidino or guanidino and X^{12} is -X^{14}-X^{15}-X^{16}-, wherein X^{15} is 1,4-phenylene or 1,4-piperidylene, X^{14} is (C_{n14})alkylene and X^{16} is (C_{n16})alkylene, wherein the sum of n14 and n16 is 0, 1 or 2; and R^2 is R^8-X^{20}- or R^9-X^{21}-, wherein R^8 is amino or methylamino, X^{20} is -X^{22}-X^{23}-X^{24}-, wherein X^{23} is *trans*-1,4-cyclohexylene or 1,4-phenylene, X^{22} is (C_{n22})alkylene and X^{16} is (C_{n24})alkylene, wherein the sum of n22 and n24 is 1 or 2, R^9 is imidazol-1-yl, imidazol-4-yl, 4-methylimidazol-1-yl, 5-methylimidazol-1-yl, piperid-4-yl or pyrid-4-yl and X^{21} is (C_{1-5})alkylene or 3-azatrimethylene; and the pharmaceutically acceptable salts, *N*-oxides, prodrug derivatives and protected derivatives thereof.

Particularly preferred compounds of Formula I are those in which X^5 is *cis*-1,5-cyclooctylene and X^4 and X^6 each are a covalent bond; X^1 and X^9 are independently -C(O)- or -NHC(O)-; X^3 and X^7 each are -C(O)O-; X^2 and X^8 are independently -X^{10}-X^{11}-, wherein X^{10} is a covalent bond and X^{11} is 1,4-piperazinylene; R^1 is R^4-X^{12}-, wherein R^4 is amidino or guanidino and X^{12} is -X^{14}-X^{15}-X^{16}-, wherein X^{15} is 1,4-phenylene, X^{14} is a covalent bond and X^{16} is methylene; and R^2 is R^8-X^{20}- or R^9-X^{21}-, wherein R^8 is amino, X^{20} is -X^{22}-X^{23}-X^{24}-, wherein X^{23} is *trans*-1,4-cyclohexylene, X^{22} is a covalent bond and X^{24} is methylene, R^9 is piperid-4-yl and X^{21} is ethylene or trimethylene; and the pharmaceutically acceptable salts, *N*-oxides, prodrug derivatives and protected derivatives thereof.

Particularly preferred compounds of Formula I are those in which X^4-X^5-X^6 together are (C_{4-8})alkylene; X^1 and X^9 are independently -C(O)- or -NHC(O)-; X^3 and X^7 are independently -C(O)- or -C(O)O-; X^2 and X^8 each are -X^{10}-X^{11}-, wherein X^{10} is a covalent bond and X^{11} is 1,4-piperazinylene; R^1 is R^4-X^{12}-, wherein R^4 is amidino or guanidino and X^{12} is -X^{14}-X^{15}-X^{16}-, wherein X^{15} is 1,4-phenylene, X^{14} is a covalent bond and X^{16} is methylene; and R^2 is R^8-X^{20}-, wherein R^8 is amidino or guanidino and X^{20} is -X^{22}-X^{23}-X^{24}-, wherein X^{23} is 1,4-phenylene, X^{22} is a covalent bond and X^{24} is methylene; and the pharmaceutically acceptable salts, *N*-oxides, prodrug derivatives and protected derivatives thereof.

Most preferred compounds of Formula I are the following:

4-guanidinobenzyl 4-{7-[4-(4-guanidinobenzylcarbamoyl)piperazin-1-ylcarbonyl]-heptanoyl}-1-piperazinecarboxamide;

4-guanidinobenzyl 4-{8-[4-(4-guanidinobenzylcarbamoyl)piperazin-1-ylcarbonyl]octanoyl}-1-piperazinecarboxamide;

4-guanidinobenzyl 4-{9-[4-(4-guanidinobenzylcarbamoyl)piperazin-1-ylcarbonyl]-nonanoyl}-1-piperazinecarboxamide;

4-amidinobenzyl 4-{7-[4-(4-amidinobenzylcarbamoyl)piperazin-1-ylcarbonyl]heptanoyl}-1-piperazinecarboxamide;

cis-1,5-cyclooctylene 4-(4-amidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-(2-piperid-4-ylethylcarbamoyl)-1-piperazinecarboxylate;

1,5-pentamethylene di[4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate];

cis-1,5-cyclooctylene 4-(4-amidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-(4-piperid-4-ylbutyryl)-1-piperazinecarboxylate;

cis-1,5-cyclooctylene *trans*-4-(4-aminocyclohexylmethylcarbamoyl)-1-piperazinecarboxylate 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate;

cis-1,5-cyclooctylene 4-(4-amidinophenylacetyl)-1-piperazinecarboxylate 4-(4-piperid-4-ylbutyryl)-1-piperazinecarboxylate;

1,4-tetramethylene di[4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate];

cis-1,5-cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-(2-piperid-4-ylethylcarbamoyl)-1-piperazinecarboxylate;

4-guanidinobenzyl 4-{6-[4-(4-guanidinobenzylcarbamoyl)piperazin-1-ylcarbonyl]hexanoyl}-1-piperazinecarboxamide;

cis-1,5-cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-(4-piperid-4-ylbutyryl)-1-piperazinecarboxylate;

cis-1,5-cyclooctylene 4-(4-guanidinophenylacetyl)-1-piperazinecarboxylate 4-(2-piperid-4-ylethylcarbamoyl)-1-piperazinecarboxylate;

cis-1,5-cyclooctylene 4-(4-guanidinophenylacetyl)-1-piperazinecarboxylate 4-(4-piperid-4-ylbutyryl)-1-piperazinecarboxylate;

4-guanidinobenzyl 4-{5-[4-(4-guanidinobenzylcarbamoyl)piperazin-1-ylcarbonyl]valeryl}-1-piperazinecarboxamide;

3-oxa-1,5-pentamethylene di[4-(4-guanidinophenylacetyl)piperazin-1-ylcarbonyl]; and

cis-1,5-cyclooctylene 4-(4-amidinophenylacetyl)-1-piperazinecarboxylate 4-(2-piperid-4-ylethylcarbamoyl)-1-piperazinecarboxylate; and the pharmaceutically acceptable salts, *N*-oxides, prodrug derivatives and protected derivatives thereof.

Pharmacology and Utility:

The compounds of this invention are tryptase inhibitors. As such the compounds of Formula I are useful for treating diseases, particularly immunomediated inflammatory diseases in which tryptase activity contributes to the pathology and/or symptomatology of the disease. For example, immunomediated inflammatory diseases in which tryptase activity contributes to its pathology and/or symptomatology include asthma, allergic rhinitis, rheumatoid spodylitis, osteoarthritis, gouty arthritis, rheumatoid arthritis, arthritic conditions in general, urticaria, angioedema, eczematous dermatitis, anaphylaxis, hyper proliferative skin disease, peptic ulcers, inflammatory bowel disease, ocular and vernal conjunctivitis, inflammatory skin conditions, and the like.

Suitable *in vitro* assays for measuring tryptase activity and the inhibition thereof by compounds are known (e.g., see Sturzebecher *et al.* (1992) *Biol. Chem. Hoppe-Seyler* 373:1025-1030). Typically, the assay will measures tryptase induced hydrolysis of peptide base substrate. For further details of an *in vitro* assay for measuring tryptase activity see Example 33, infra.

Suitable *in vivo* models of inflammation are known to those of ordinary skill in the art. For example, *in vivo* models for asthma are known (e.g., see Larsen (1991) *Experimental Models of Reversible Airway Obstruction.* In: West *et al.*, eds. *The Lung: Scientific Foundations* Raven Press, New York). For further details of an *in vitro* model of asthma see Example 2, infra. Further, *in vivo* models of inflammatory skin conditions (Walsh *et al.* (1995) *Br. J. Pharmacol.*

114: 1343-1350; and Armstrong *et al.* (1995) *Prostaglandins* 49: 205-224), arthritic conditions (Peacock *et al.* (1995) *Cell Immunol.* 160: 178-184; and Houri *et al.* (1995) *Curr. Opin. Rheumatol.* 7: 201-205) and gastrointestinal diseases (Anthony *et al.* (1995) *Int. J. Exp. Pathol.* 76: 215-224.; and Carter *et al.* (1995) *Dig. Dis.Sci.* 40: 192-197) are known. For further details of an *in vivo* assay for measuring asthmatic responses see Example 34, infra.

Administration and Pharmaceutical Compositions:

In general, compounds of Formula I will be administered in therapeutically effective amounts via any of the usual and acceptable modes known in the art, either singly or in combination with another therapeutic agent. A therapeutically effective amount may vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. For example, therapeutically effective amounts of a compound of Formula I for the treatment of asthma may range from 0.1 micrograms per kilogram body weight (μg/kg) per day to 1 milligram per kilogram body weight (mg/kg) per day, typically 1 μg/kg/day to 0.1 mg/kg/day. Therefore, a therapeutically effective amount for a 80 kg asthmatic human patient may range from 10 μg/day to 10 mg/day, typically 0.1 mg/day to 10 mg/day.

Therapeutic agents that may be useful for administration in combination with compounds of Formula I in treating asthma include β-adrenergic agonists (e.g., albuterol, terbutaline, formoterol, fenoterol, prenaline and the like), methylxanthines (e.g., caffeine, theophylline, aminophylline, theobromine and the like), cromoglycates (e.g., cromolyn, nedocromil, and the like) and corticosteroids (e.g., beclomethasome, triamcinolone, flurisolide, dexamethasone and the like). In general, one of ordinary skill in the art, acting in reliance upon personal knowledge and the disclosure of this application, will be able to ascertain a therapeutically effective amount of a compound of Formula I for treating a given inflammatory disease.

The compounds of Formula I can be administered as pharmaceutical compositions by one of the following routes: oral, systemic (e.g., transdermal, intranasal or by suppository) or parenteral (e.g., intramuscular, intravenous or subcutaneous). Compositions can take the form of tablets, pills, capsules, semisolids, powders, sustained release formulations, solutions, suspensions, elixirs, aerosols, or any other appropriate composition and are comprised of, in general, a compound of Formula I in combination with at least one pharmaceutically acceptable excipient. Acceptable excipients are non-toxic, aid administration, and do not adversely affect the therapeutic benefit of the active ingredient. Such excipient may be any solid, liquid, semisolid or, in the case of an aerosol composition, gaseous excipient that is generally available to one of skill in the art.

Solid pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, sucrose,

gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk, and the like. Liquid and semisolid excipients may be selected from water, ethanol, glycerol, propylene glycol and various oils, including those of petroleum, animal, vegetable or synthetic origin (e.g., peanut oil, soybean oil, mineral oil, sesame oil, etc.). Preferred liquid carriers, particularly for injectable solutions, include water, saline, aqueous dextrose and glycols.

Compressed gases may be used to disperse the active ingredient in aerosol form. Inert gases suitable for this purpose are nitrogen, carbon dioxide, nitrous oxide, etc. Other suitable pharmaceutical carriers and their formulations are described in A.R. Alfonso *Remington's Pharmaceutical Sciences* 1985, 17th ed. Easton, Pa.: Mack Publishing Company.

The amount of a compound of Formula I in the composition may vary widely depending upon the type of formulation, size of a unit dosage, kind of excipients and other factors known to those of skill in the art of pharmaceutical sciences. In general, a composition of a compound of Formula I for treating asthma will comprise from 0.01%w to 10%w, preferably 0.3%w to 1%w, of active ingredient with the remainder being the excipient or excipients. Preferably the pharmaceutical composition is administered in a single unit dosage form for continuous treatment or in a single unit dosage form ad libitum when relief of symptoms is specifically required. Representative pharmaceutical formulations containing a compound of Formula I arc described in Example 34.

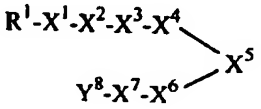
Chemistry:

The compounds of the invention are comprised of five distinct subunits (i.e., R^1-, $-X^2-$, $-X^4-X^5-X^6-$, $-X^8-$ and R^2-) which subunits are connected via carbonyl, formyloxy, amide, sulfonamide, carbamate or urea linkages (i.e., -C(O)-, -C(O)O-, -OC(O)-, $-C(O)N(R^3)-$, $-N(R^3)C(O)-$, $-S(O)_2N(R^3)-$, $-N(R^3)S(O)_2-$, $-OC(O)N(R^3)-$, $-N(R^3)C(O)O-$, $-N(R^3)C(O)N(R^3)-$ or -OC(O)O-). Methods for forming such linking groups are known and suitable reagents are readily available (e.g., see, March, *Advanced Organic Chemistry*, 4th Ed. (Wiley 1992); Larock, *Comprehensive Organic Transformations* (VCH 1989); and Furniss *et al.*, *Vogel's Textbook of Practical Organic Chemistry*, 5th Ed.. (Longman 1989).

The subunits comprising the compounds of Formula I can be assembled individually or as

larger combinations of subunits. The following reaction schemes are representative methods for preparing compounds of Formula I. It is understood that the compounds of Formula I can be prepared by other analogous procedures.

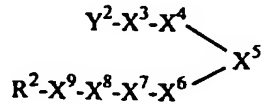
Compounds of Formula I in which X^8 is 1,4-piperazinylene or 1,4-piperidylene and X^9 is -C(O)-, -OC(O)- or -N(R^3)C(O)- or in which X^8 is (C_{1-8})alkylene and X^9 is -C(O)N(R^3)-, -OC(O)N(R^3)- or -N(R^3)C(O)N(R^3)- can be prepared by reacting a compound of Formula 1:



1

or a protected derivative thereof, with a compound of the formula R^2-Y^9-C(O)L, or a protected derivative thereof, wherein L is a leaving group, Y^9 is a bond, -O- or -N(R^3)-, Y^8 is piperazin-1-yl, piperid-4-yl or HN(R^3)-(C_{1-8})alkyl, respectively, and each R^1, R^2, R^3, X^1, X^2, X^3, X^4, X^5, X^6 and X^7 are as defined in the Summary of the Invention, and then deprotecting when necessary. Alternatively, compounds of Formula I in which X^8 is 1,4-piperazinylene or 1,4-piperidylene and X^9 is -NHC(O)- or in which X^8 is (C_{1-8})alkylene and X^9 is -NHC(O)N(R^3)- can be prepared by reacting an appropriate compound of Formula 1, or a protected derivative thereof, with an isocyanate of the formula R^2-NC(O), or a protected derivative thereof, and then deprotecting when necessary (for further details see Example 8, infra.).

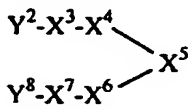
In an analogous fashion, compounds of Formula I in which X^2 is 1,4-piperazinylene or 1,4-piperidylene and X^1 is -C(O)-, -OC(O)- or -N(R^3)C(O)- or in which X^2 is (C_{1-8})alkylene and X^1 is -C(O)N(R^3)-, -OC(O)N(R^3)- or -N(R^3)C(O)N(R^3)- can be prepared by reacting a compound of Formula 2:



2

or a protected derivative thereof, with a compound of the formula R^1-Y^1-C(O)L, or a protected derivative thereof, wherein L is a leaving group, Y^1 is a bond, -O- or -N(R^3)-, Y^2 is piperazin-1-yl, piperid-4-yl or HN(R^3)-(C_{1-8})alkyl, respectively, and each R^1, R^2, R^3, X^3, X^4, X^5, X^6, X^7, X^8 and X^9 are as defined in the Summary of the Invention, and then deprotecting when necessary. Alternatively, compounds of Formula I in which X^2 is 1,4-piperazinylene or 1,4-piperidylene and X^1 is -NHC(O)- or in which X^2 is (C_{1-8})alkylene and X^1 is -NHC(O)N(R^3)- can be prepared by reacting a compound of Formula 2, or a protected derivative thereof, with an isocyanate of the formula R^1-NC(O), or a protected derivative thereof, and then deprotecting when necessary (for further details see Example 14(b), infra.).

Compounds of Formula I in which R^1 equals R^2; X^2 and/or X^8 is 1,4-piperazinylene or 1,4-piperidylene; X^1 is -C(O)-, -OC(O)- or -N(R^3)C(O)-; and X^9 is -C(O)-, -OC(O)- or -N(R^3)C(O)- and/or in which X^2 and/or X^8 is (C_{1-8})alkylene; X^1 is -C(O)N(R^3)-, -OC(O)N(R^3)- or -N(R^3)C(O)N(R^3)-; and X^9 -C(O)N(R^3)-, -OC(O)N(R^3)- or -N(R^3)C(O)N(R^3)- can be prepared by reacting a compound of Formula 3:

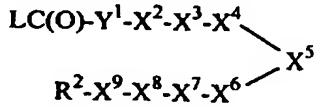


3

or a protected derivative thereof, with 2 or more molar equivalents of a compound of the formula R^1-Y^1-C(O)L, or a protected derivative thereof, wherein L is a leaving group, Y^1 is a bond, -O- or -N(R^3)-, Y^2 and Y^8 are independently piperazin-1-yl, piperid-4-yl or HN(R^3)-(C_{1-8})alkyl and each R^1, R^3, X^3, X^4, X^5, X^6 and X^7 are as defined in the Summary of the Invention, and then deprotecting when necessary. Alternatively, compounds of Formula I in which R^1 equals R^2; X^2 and/or X^8 is 1,4-piperazinylene or 1,4-piperidylene; X^1 is -NHC(O)- and/or X^9 is -NHC(O)- and/or in which X^2 and/or X^8 is (C_{1-8})alkylene and X^1 is -NHC(O)N(R^3)- and/or X^9 is -NHC(O)N(R^3)- can be prepared by reacting a compound of Formula 3, or a protected derivative thereof, with two or more molar equivalents of an isocyanate of the formula R^1-NC(O), or a protected derivative thereof, and then deprotecting when necessary (for further details see

Example 10, infra.).

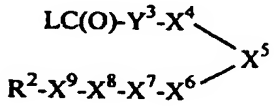
Compounds of Formula I in which X^1 is $-N(R^3)C(O)-$, $-N(R^3)C(O)O-$ or $-N(R^3)C(O)N(R^3)-$ can be prepared by reacting an amine of the formula $R^1-N(R^3)H$, or a protected derivative thereof, with a compound of Formula 4:



4

or a protected derivative, wherein L is a leaving group, Y^1 is a bond, -O- or $-N(R^3)-$ and each R^1, R^2, R^3, X^2, X^3, X^4, X^5, X^6, X^7, X^8 and X^9 are as defined in the Summary of the Invention (for further details see Example 20, infra.).

Compounds of Formula I in which X^2 is 1,4-piperazinylene or 4,1-piperidylene and X^3 is -C(O)-, -C(O)O- or $-C(O)N(R^3)-$ or in which X^2 is (C_{1-8})alkylene and X^3 is $-N(R^3)C(O)-$, $-N(R^3)C(O)O-$ or $-N(R^3)C(O)N(R^3)-$ can be prepared by reacting a compound of the formula $R^1-X^1-Y^2$, or a protected derivative thereof, with a compound of Formula 5:

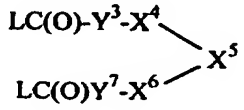


5

or a protected derivative thereof, wherein L is a leaving group, Y^3 is a bond, -O- or $-N(R^3)-$, Y^2 is piperazin-1-yl, piperid-4-yl or $HN(R^3)-(C_{1-8})$alkyl, respectively, and each R^1, R^2, R^3, X^1, X^2, X^3, X^4, X^5, X^6, X^7, X^8 and X^9 are as defined in the Summary of the Invention (for further details see Example 31, infra.).

Compounds of Formula I in which X^2 and X^8 each are 1,4-piperazinylene or 4,1-piperidylene and X^3 and X^7 are independently -C(O)-, -C(O)O- or $-C(O)N(R^3)-$ or in which X^2 and X^8 each are (C_{1-8})alkylene or hetero(C_{1-8})alkylene and X^3 and X^7 are independently

$-N(R^3)C(O)-$, $-N(R^3)C(O)O-$ or $-N(R^3)C(O)N(R^3)-$ can be prepared by reacting two or more molar equivalents of a compound of the formula $R^1-X^1-Y^2$, or a protected derivative thereof, with a compound of Formula 6:



6

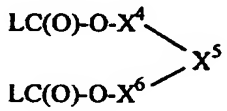
or a protected derivative thereof, wherein L is a leaving group, Y^3 and Y^7 are independently a bond, -O- or $-N(R^3)-$, Y^2 is piperazin-1-yl, piperid-4-yl, $HN(R^3)-(C_{1-8})$alkyl or $HN(R^3)$-hetero(C_{1-8})alkyl, respectively, and each R^1, X^1, X^4, X^5 and X^6 are as defined in the Summary of the Invention (for further details see Example 32, infra.).

The acylation reactions described above can be carried out by reacting together an activated ester (e.g., an acid chloride derivative) and an appropriate nucleophile in the presence of a suitable organic base (e.g., *N,N*-diisopropylethylamine (DIEA), *N*-methylmorpholine, etc. preferably DIEA) and suitable solvent (e.g., *N,N*-dimethylformamide (DMF), tetrahydrofuran (THF), dichloromethane, etc.) at 20 to 30°C, typically at approximately 23°C, for several minutes to 24 hours. Alternatively, the acylation can be effected by reacting together an appropriate carboxylic acid and nucleophile in the presence of a suitable coupling reagent (e.g., 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, etc.) and a suitable solvent (e.g., DMF, etc.) at 20 to 30°C, typically at approximately 23°C, for several hours to several days. The reactions described above for the preparation of compounds of Formula I and the conditions for effecting the reactions are illustrative and one of ordinary skill in the art will recognize that other reaction conditions can be applied and different starting materials can be used to prepare the compounds of the invention.

Deprotection can be effected by any means which removes the protective group and gives the desired product in reasonable yield. A detailed description of the techniques applicable to the creation of protective groups and their removal can be found in T.W. Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc. 1981.

Generally, the starting materials useful in preparing the compounds of Formula I and the intermediates useful in preparing the compounds of Formula I are commercially available or can be readily prepared by those of ordinary skill in the art. For example, intermediates useful in preparing the compounds of Formula I are conveniently prepared by the acylation reactions described above. When necessary suitable protection chemistry is employed to direct the reaction to the desired reactive site when multiple reactive sites are present in the starting materials.

A convenient starting material for preparing compounds of Formula I in which X^3 and X^7 each are -C(O)O- is a compound of Formula 7:



7

in which each X^4, X^5 and X^6 are as defined in the Summary of the Invention. For example, compounds of Formula 6 in which L is chloro can be prepared by reacting a corresponding diol (e.g., cis-1,5-cyclooctanediol, trans-1,4-cyclohexylendimethanol, 1,4-phenylenedimethanol, etc.) with triphosgene (for further details see Example 5, infra.).

Intermediates useful in preparing compounds of Formula I in which such intermediate contains a amidino group can be prepared by treating a corresponding nitrile with hydrogen chloride in ethanol and then reacting with ammonia.

Additional Processes for Preparing Compounds of Formula I:

Compounds of Formula I in which R^4 is guanidino can be prepared by reacting a corresponding compound of Formula I in which R^4 is amino with cyanamide. The reaction is carried out by treating the amine with hydrogen chloride and then reacting neat with an excess of cyanamide at approximately 65°C for about two hours (for further details see Example 15, infra.).

Compounds of Formula I may be prepared as pharmaceutically acceptable acid addition

salts by reacting the free base forms of a compound of Formula I with a pharmaceutically acceptable inorganic or organic acid. Alternatively, the pharmaceutically acceptable base addition salts of compounds of Formula I may be prepared by reacting the free acid forms of compounds of Formula I with pharmaceutically acceptable inorganic or organic bases. Inorganic and organic acids and bases suitable for the preparation of the pharmaceutically acceptable salts of compounds of Formula I are set forth in the definitions section of this application. Alternatively, the salt forms of the compounds of Formula I may be prepared using salts of the starting materials or intermediates.

The free acid or free base forms of the compounds of Formula I can be prepared from the corresponding base addition salt or acid addition salt form. For example, compounds of Formula I in an acid addition salt form may be converted to the corresponding free base by treating with a suitable base (e.g., ammonium hydroxide solution, sodium hydroxide, etc.). Compounds of Formula I in a base addition salt form may be converted to the corresponding free acid by treating with a suitable acid (e.g., hydrochloric acid, etc).

The *N*-oxides of compounds of Formula I can be prepared by methods known to those of ordinary skill in the art. For example, *N*-oxides can be prepared by treating an unoxidized form of the compound of Formula I with an oxidizing agent (e.g., trifluoroperacetic acid, permaleic acid, perbenzoic acid, peracetic acid, *meta*-chloroperoxybenzoic acid, etc.) in a suitable inert organic solvent (e.g., a halogenated hydrocarbon such as methylene chloride) at approximately 0°C. Alternatively, the *N*-oxides of the compounds of Formula I can be prepared from the *N*-oxide of an appropriate starting material.

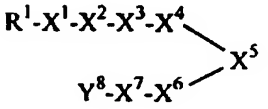
Compounds of Formula I in unoxidized form can be prepared from *N*-oxides of compounds of Formula I by treating with a reducing agent (e.g., sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, phosphorus trichloride, tribromide, etc.) in an suitable inert organic solvent (e.g., acetonitrile, ethanol, aqueous dioxane, etc.) at 0 to 80°C.

Prodrug derivatives of the compounds of Formula I can be prepared by methods known to those of ordinary skill in the art (e.g., for further details see Saulnier *et al.*(1994), *Bioorganic and Medicinal Chemistry Letters*. 4:1985). For example, appropriate prodrugs can be prepared by reacting a non-derivatized compound of Formula I with a suitable carbamylating agent (e.g., 1,1-acyloxyalkylcarbonochloridate, *para*-nitrophenyl carbonate, etc.).

Protected derivatives of the compounds of Formula I can be made by means known to those of ordinary skill in the art. A detailed description of the techniques applicable to the creation of protective groups and their removal can be found in T.W. Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc. 1981.

In summary, an aspect of this invention is a process for preparing compounds of Formula I, which process comprises:

(a) reacting a compound of Formula 1:

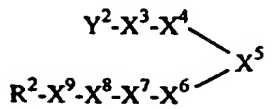


1

or a protected derivative thereof, with a compound of the formula R^2-Y^9-C(O)L, or a protected derivative thereof, wherein L is a leaving group, Y^9 is a bond, -O- or -N(R^3)-, Y^8 is piperazin-1-yl, piperid-4-yl or HN(R^3)-(C_{1-8})alkyl, respectively, and each R^1, R^2, R^3, X^1, X^2, X^3, X^4, X^5, X^6 and X^7 are as defined in the Summary of the Invention, and then deprotecting when necessary, to give a compound of Formula I, in which X^8 is 1,4-piperazinylene or 1,4-piperidylene and X^9 is -C(O)-, -OC(O)- or -N(R^3)C(O)- or in which X^8 is (C_{1-8})alkylene and X^9 is -C(O)N(R^3)-, -OC(O)N(R^3)- or -N(R^3)C(O)N(R^3)-;

(b) reacting a compound of Formula 1, or a protected derivative thereof, with an isocyanate of the formula R^2-NC(O), or a protected derivative thereof, and then deprotecting when necessary, to give a compound of Formula I in which X^8 is 1,4-piperazinylene or 1,4-piperidylene and X^9 is -NHC(O)- or in which X^8 is (C_{1-8})alkylene and X^9 is -NHC(O)N(R^3)-;

(c) reacting a compound of Formula 2:

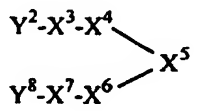


2

or a protected derivative thereof, with a compound of the formula R^1-Y^1-C(O)L, or a protected derivative thereof, wherein L is a leaving group, Y^1 is a bond, -O- or -N(R^3)-, Y^2 is piperazin-1-yl, piperid-4-yl or HN(R^3)-(C_{1-8})alkyl, respectively, and each R^1, R^2, R^3, X^3, X^4, X^5, X^6, X^7, X^8 and X^9 are as defined in the Summary of the Invention, and then deprotecting when necessary, to give a compound of Formula I in which X^2 is 1,4-piperazinylene or 1,4-piperidylene and X^1 is -C(O)-, -OC(O)- or -N(R^3)C(O)- or in which X^2 is (C_{1-8})alkylene and X^1 is -C(O)N(R^3)-, -OC(O)N(R^3)- or -N(R^3)C(O)N(R^3)-;

(d) reacting a compound of Formula 2, or a protected derivative thereof, with an isocyanate of the formula R^1-NC(O), or a protected derivative thereof, and then deprotecting when necessary, to give a compound of Formula I in which X^2 is 1,4-piperazinylene or 1,4-piperidylene and X^1 is -NHC(O)- or in which X^2 is (C_{1-8})alkylene and X^1 is -NHC(O)N(R^3)-;

(e) reacting a compound of Formula 3:



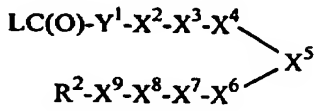
3

or a protected derivative thereof, with 2 or more molar equivalents of a compound of the formula R^1-Y^1-C(O)L, or a protected derivative thereof, wherein L is a leaving group, Y^1 is a bond, -O- or -N(R^3)-, Y^2 and Y^8 are independently piperazin-1-yl, piperid-4-yl or HN(R^3)-(C_{1-8})alkyl and each R^1, R^3, X^3, X^4, X^5, X^6 and X^7 are as defined in the Summary of the Invention, and then deprotecting when necessary, to give a compound of Formula I in which R^1 equals R^2; X^2 and/or X^8 is 1,4-piperazinylene or 1,4-piperidylene; X^1 is -C(O)-, -OC(O)- or -N(R^3)C(O)-; and X^9 is -C(O)-, -OC(O)- or -N(R^3)C(O)- and/or in which X^2 and/or X^8 is (C_{1-8})alkylene; X^1 is -C(O)N(R^3)-, -OC(O)N(R^3)- or -N(R^3)C(O)N(R^3)-; and X^9 -C(O)N(R^3)-, -OC(O)N(R^3)- or -N(R^3)C(O)N(R^3)-;

(f) reacting a compound of Formula 3, or a protected derivative thereof, with two or more molar equivalents of an isocyanate of the formula R^1-NC(O), or a protected derivative thereof, and then deprotecting when necessary, to give a compound of Formula I in which R^1 equals R^2;

X^2 and/or X^8 is 1,4-piperazinylene or 1,4-piperidylene; X^1 is -NHC(O)- and/or X^9 is -NHC(O)- and/or in which X^2 and/or X^8 is (C_{1-8})alkylene and X^1 is -NHC(O)N(R^3)- and/or X^9 is -NHC(O)N(R^3)-;

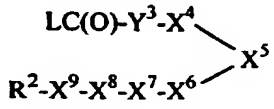
(g) reacting an amine of the formula R^1-N(R^3)H, or a protected derivative thereof, with a compound Formula 4:



4

or a protected derivative thereof, wherein L is a leaving group, Y^1 is a bond, -O- or -N(R^3)- and each R^1, R^2, R^3, X^2, X^3, X^4, X^5, X^6, X^7, X^8 and X^9 are as defined in the Summary of the Invention, and then deprotecting when necessary, to give a compound of Formula I in which X^1 is -N(R^3)C(O)-, -N(R^3)C(O)O- or -N(R^3)C(O)N(R^3)-;

(h) reacting a compound of the formula R^1-X^1-Y^2, or a protected derivative thereof, with a compound of Formula 5:

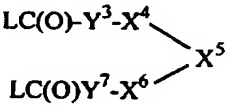


5

or a protected derivative thereof, wherein L is a leaving group, Y^3 is a bond, -O- or -N(R^3)-, Y^2 is piperazin-1-yl, piperid-4-yl or HN(R^3)-(C_{1-8})alkyl, respectively, and each R^1, R^2, R^3, X^1, X^2, X^3, X^4, X^5, X^6, X^7, X^8 and X^9 are as defined in the Summary of the Invention, and then deprotecting when necessary, to give a compound of Formula I in which X^2 is 1,4-piperazinylene or 4,1-piperidylene and X^3 is -C(O)-, -C(O)O- or -C(O)N(R^3)- or in which X^2 is (C_{1-8})alkylene and X^3 is -N(R^3)C(O)-, -N(R^3)C(O)O- or -N(R^3)C(O)N(R^3)-;

(i) reacting 2 or more molar equivalents of compound of the formula R^1-X^1-Y^2, or a

protected derivative thereof, with a compound of Formula 6:



6

or a protected derivative thereof, wherein L is a leaving group, Y^3 and Y^7 are independently a bond, -O- or -N(R^3)-, Y^2 is piperazin-1-yl, piperid-4-yl, HN(R^3)-(C_{1-8})alkyl or HN(R^3)-hetero(C_{1-8})alkyl and each R^1, X^1, X^4, X^5 and X^6 are as defined in the Summary of the Invention, and then deprotecting when necessary, to give a compound of Formula I in which X^2 and X^8 each are 1,4-piperazinylene or 4,1-piperidylene and X^3 and X^7 are independently -C(O)-, -C(O)O- or -C(O)N(R^3)- or in which X^2 and X^8 each are (C_{1-8})alkylene or hetero(C_{1-8})alkylene and X^3 and X^2 are independently -N(R^3)C(O)-, -N(R^3)C(O)O- or -N(R^3)C(O)N(R^3)-, respectively;

(j) optionally reacting a compound of Formula I in which R^4 is amino with cyanamide to give a compound of Formula I in which R^4 is guanidino;

(k) optionally further converting a compound of Formula I into a pharmaceutically acceptable salt;

(l) optionally further converting a salt form of a compound of Formula I to non-salt form;

(m) optionally further converting an unoxidized form of a compound of Formula I into a pharmaceutically acceptable *N*-oxide;

(n) optionally further an *N*-oxide form of a compound of Formula I its unoxidized form;

(o) optionally further converting a non-derivatized compound of Formula I into a pharmaceutically prodrug derivative; and

(p) optionally further converting a prodrug derivative of a compound of Formula I to its non-derivatized form.

In any of the above processes, a reference to Formula I refers to such Formula wherein each R^1, R^2, R^3, X^1, X^2, X^3, X^4, X^5, X^6, X^7 X^8 and X^9 are as defined in their broadest definiti ns set forth in the Summary of the Invention, with the processes applying particularly well to the presently preferred embodiments.

Examples:

EXAMPLE 1

tert-Butyl 4-aminobenzylcarbamate hydrochloride

4-Aminobenzylamine (50.34 g, 0.412 mol) in dichloromethane (200 mL) was placed in a one liter 3 neck round bottom flask fitted with a mechanical stirring apparatus and the solution was cooled to 0°C. di-*tert*-Butyl dicarbonate (89.9 g, 0.412 mol.) in dichloromethane (200 mL) was added dropwise to the solution over 30 minutes and the resulting suspension was stirred 2 hours at 0°C giving a nearly homogeneous solution. The dichloromethane solution subsequently was washed with aqueous sodium hydroxide (1.0 M, 500 mL) and then water (500 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* giving a yellow oil. The oil was taken into ethyl ether : methanol (2:1, 225 mL) and the solution was cooled to 0°C, acidified with hydrogen chloride in dioxane (4.0 M, 115 mL, 0.412 mol.) and combined with ethyl ether (200 mL) giving a thick pale yellow precipitate. The precipitate was collected by filtration and washed with additional ethyl ether (500 mL). Drying *in vacuo* gave *tert*-butyl 4-aminobenzylcarbamate hydrochloride (100.23 g, 0.387 mol, 94% yield) as a pale yellow solid; ^{1}H-NMR (300MHz, DMSO-d_6): 10.40-10.20 (br s, 3H), 7.40 (tr, 1H), 7.30 (s, 4H), 4.10 (d, 2H), 1.40 (s, 9H).

EXAMPLE 2

tert-Butyl 4-guanidinobenzylcarbamate

Cyanamide (100 g, 2.4 mol) was placed in a 500 mL round bottom flask and heated to between 60 and 65°C until the material completely melted and then *tert*-butyl 4-aminobenzylcarbamate hydrochloride (25.3 g, 97.8 mmol.), prepared as in Example 1, was added directly to the liquid cyanamide giving a yellow solution. The solution was stirred 2 hours at between 60 and 65°C and then water (100 mL) was added. The aqueous mixture was cooled to room temperature and washed with ethyl ether (1 L). The organic phase was back extracted with water (2x, 100 mL) and the combined aqueous layers were washed with ethyl ether (500

mL), cooled in an ice water bath and then basified with aqueous sodium hydroxide (10 M, 100 mL) giving an insoluble oil which slowly crystallized. The crystals were collected by filtration washed with water. Drying *in vacuo* gave *tert*-butyl 4-guanidinobenzylcarbamate (18.3 g, 69.24 mmol, 70.8% yield) as a colorless crystalline solid; ^{1}H-NMR (300MHz, DMSO-d_6): 9.70 (s, 1H), 7.42 (tr, 1H), 7.40 (s, 4H), 7.25 (d, 2H), 7.15 (d, 2H), 4.10 (d, 2H), 1.40 (s, 9H).

EXAMPLE 3

tert-Butyl 4-chlorocarbonyl-1-piperazinecarboxylate

Triphosgene (25 g, 84.2 mmol) was taken into dichloromethane (200 mL) and the resulting solution cooled to 0°C. A mixture of *tert*-butyl 1-piperazinecarboxylate (40 g, 214.8 mmol) and pyridine (35 mL, 432.7 mmol) in dichloromethane (100 mL) then was added dropwise to the triphosgene solution and the reaction mixture was allowed to warm to room temperature over 30 minutes. The mixture was quenched with aqueous hydrochloric acid (0.1N, 200 mL) and the aqueous phase was washed with dichloromethane (50 mL). The combined organic layers were dried ($MgSO_4$) and filtered. Concentrating *in vacuo* gave *tert*-butyl 4-chlorocarbonyl-1-piperazinecarboxylate (45.6 g, 71.6 mmol, 85% yield) as a yellow solid; ^{1}H-NMR (300MHz, $CDCl_3$): 3.70 (m, 2H), 3.60 (m, 2H), 3.50 (m, 4H), 1.50 (s, 9H).

EXAMPLE 4

tert-Butyl 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate trifluoroacetate

tert-Butyl 4-guanidinobenzylcarbamate (41.77 g, 0.158 mol.), prepared as in Example 2, was treated with trifluoroacetic acid (TFA) (100 mL) for 30 minutes at room temperature. The resulting nearly colorless liquid was concentrated *in vacuo* at 45°C and the residue was triturated with ethyl ether (3x, 400 mL) and dried *in vacuo* to a colorless foam. The residue was dissolved in methanol (200 mL) and then DIEA (55 mL, 0.32 mol, amount based on estimated excess TFA present) was added to the solution. The mixture was cooled to 0°C and then *tert*-butyl 4-chlorocarbonyl-1-piperazinecarboxylate (39.3 g, 0.158 mol.), prepared as in Example 3, in

dichloromethane (120 mL) was added. An additional amount of DIEA (30 mL) was added and the reaction mixture was allowed to warm to room temperature, stirred 12 hours and concentrated *in vacuo* giving an orange oil. The oil was combined with water (200 mL) giving a thick precipitate. Recrystallization of the precipitate from acetonitrile and ether gave *tert*-butyl 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate trifluoroacetate (62.0 g, 0.126 mol, 80% yield) as a pale yellow solid; ^{1}H-NMR (300MHz, DMSO-d_6): 10.15 (s, 1H), 9.10 (br s, 2H), 7.65 (s, 4H), 7.40 (tr, 1H), 7.25 (dd AB, 4H), 4.25 (d, 2H), 3.55 (m, 4H), 3.10 (s, 4H); Electrospray LRMS: Calculated for $C_{13}H_{20}N_6O$: MH^+: 277.4; $MH_2^{+2}/2$: 139.2, Found: MH^+: 277.4; $MH_2^{+2}/2$: 139.3.

EXAMPLE 5

cis-1,5-Cyclooctylene di(chloroformate)

cis-1,5-Cyclooctanediol (20.2 g, 0.14 mol.) was taken into acetonitrile (250 mL) and potassium carbonate (41.4 g, 0.3 mol.) was added to the mixture giving a suspension. The suspension was cooled to 0°C under a nitrogen atmosphere and then phosgene (1.9M in toluene, 220 mL, 0.42 mol.) was added dropwise over one hour. The suspension was warmed to room temperature and stirred 12 hours and then ether (1 L) was added. The suspension was filtered free of insoluble salts and concentrated. Recrystallization of the residue from hexane gave *cis*-1,5-cyclooctylene di(chloroformate) as a colorless crystalline solid. Further purification can be effected with silica gel flash chromatography using hexane:ethyl ether (10:1) as eluent; ^{1}H-NMR (300MHz, $CDCl_3$): 5.00-4.85 (m, 2H), 2.20-1.60 (m, 12H).

EXAMPLE 6

cis-1,5-Cyclooctylene chloroformate 4-*tert*-butoxycarbonyl-1-piperazinecarboxylate

cis-1,5-Cyclooctylene di(chloroformate) (1.91 g, 7.1 mmol), prepared as in Example 5, in dichloromethane (25 mL) was added dropwise to a mixture of *tert*-butyl 1-piperazinecarboxylate (1.3 g, 7.1 mmol) and DIEA (1.3 mL, 7.1 mmol) in dichloromethane (25 mL). The mixture was stirred 15 minutes at room temperature and then a workup with 0.1M aqueous hydrochloric acid was performed. The dichloromethane layer was dried ($MgSO_4$), filtered and concentrated. Purifying from the residue by silica gel flash chromatography using ethyl ether and hexanes as eluent gave *cis*-1,5-cyclooctylene chloroformate 4-*tert*-butoxycarbonyl-1-piperazinecarboxylate (660 mg, 1.6 mmol, 22% yield) as a colorless oil; ^{1}H-NMR (300MHz, $CDCl_3$): 5.00-4.90 (m, 1H), 4.80-4.70 (m, 1H), 3.40 (s, 8H), 2.05-1.40 (m, 12), 1.40 (s, 9H).

EXAMPLE 7

cis-1,5-Cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-*tert*-butoxycarbonyl-1-piperazinecarboxylate

tert-Butyl 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate trifluoroacetate (383.7 mg, 1.06 mmol), prepared as in Example 4, was treated with trifluoroacetic acid (1 mL) neat for 10 minutes at room temperature. The mixture was concentrated *in vacuo* giving a colorless oil. The oil was then taken into water (15 mL) and the pH of the aqueous solution was adjusted to between 7 and 8 with 5M aqueous sodium hydroxide added dropwise. *cis*-1,5-Cyclooctylene chloroformate 4-*tert*-butoxycarbonyl-1-piperazinecarboxylate (444.7 mg, 1.06 mmol), prepared as in Example 6, in THF (10 mL) was added to the aqueous solution and the pH was continually adjusted with 1M aqueous sodium hydroxide added dropwise until no further change in pH was observed. The mixture was concentrated *in vacuo* removing the bulk of THF and then ethyl ether (5 mL) and 5M aqueous sodium hydroxide (sufficient to adjust the pH to 14) was added giving a thick white suspension. The suspension was allowed to stand for 15 to 30 minutes at room temperature and then the precipitate was collected by filtering and washed with water (2x, 15 mL). Drying *in vacuo* gave *cis*-1,5-cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-*tert*-butoxycarbonyl-1-piperazinecarboxylate (527 mg, 0.82 mmol, 77% yield) as a colorless solid; ^{1}H-NMR (300MHz, DMSO-d_6): 7.05 (d, 2H), 7.00 (tr, 1H), 6.70 (d, 2H), 5.10 (br, 3H), 4.65 (m, 2H), 4.15 (d, 2H), 3.30 (s, 16H), 1.90-1.40 (m, 12H), 1.40 (s, 9H).

EXAMPLE 8

cis-1,5-Cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-(2-piperid-4-ylethylcarbamoyl)-1-piperazinecarboxylate trifluoroacetate (Compound 1)

The following is the preparation of a compound of Formula I in which R^1 is 4-guanidinobenzyl, R^2 is 2-piperid-4-ylethyl, X^1 and X^9 each are -NHC(O)-, X^2 and X^8 each are 1,4-piperazinylene, X^3 and X^7 each are -C(O)O-, X^4 and X^6 each are a covalent bond and X^5 is

cis-1,5-cyclooctylene.

cis-1,5-Cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-*tert*-butoxycarbonyl-1-piperazinecarboxylate (818 mg, 1.24 mmol.), prepared as in Example 7, was treated with TFA (2 mL) neat for 10 minutes. The mixture was concentration *in vacuo* giving a colorless oil. The residue was triturated with ethyl ether (2x, 10 mL) and dried *in vacuo* giving a colorless foam. The residue was then taken into DMF (2 mL) and then DIEA (700 mL, 4.0 mmol.) and *tert*-butyl 4-(2-isocyanatoethyl)-1-piperidinecarboxylate (3.2 mL, 0.39 M in DMF, 1.25 mmol.) were added. The mixture was stirred 12 hours and then concentrated *in vacuo*. The residue was triturated with water (2x, 5 mL) and dried *in vacuo* giving a yellow solid. The solid was then treated with TFA (2 mL) and the mixture was concentrated *in vacuo*. The residue was taken into water. Purifying from the aqueous mixture by preparative reverse phase HPLC gave *cis*-1,5-cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-(2-piperid-4-ylethylcarbamoyl)-1-piperazinecarboxylate as an amorphous colorless solid; Plasma Desorption LRMS: Calculated for $C_{35}H_{55}N_{10}O_6$: MH^+: 712.9, Found: MH^+: 713.2.

Proceeding as in Example 8 and substituting different starting materials the following compounds of Formula I were prepared:

cis-1,5-cyclooctylene 4-(4-aminobenzylcarbamoyl)-1-piperazinecarboxylate 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate (Compound 2); Calculated for $C_{35}H_{50}N_{10}O_6$: MH^+: 707.9, Found: MH^+: 707.7;

cis-1,5-cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-(4-piperidylmethylcarbamoyl)-1-piperazinecarboxylate (Compound 3); Calculated for $C_{34}H_{53}N_{10}O_6$: MH^+: 698.9, Found: MH^+: 699.7;

cis-1,5-cyclooctylene 4-(*trans*-4-aminocyclohexylmethylcarbamoyl)-1-piperazinecarboxylate 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate (Compound 4); Calculated for $C_{35}H_{55}N_{10}O_6$: MH^+: 712.9, Found: MH^+: 713.6;

cis-1,5-cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate

3-piperid-4-ylpropylcarbamoyl-1-piperazinecarboxylate (Compound 5); Calculated for $C_{36}H_{58}N_{10}O_6$: MH^+: 727.9 Found: MH^+: 727.9;

4-[4-(2-piperid-4-ylethylcarbamoyl)piperazin-1-ylcarbonyl]benzyl 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate (Compound 6); Calculated for $C_{34}H_{48}N_{10}O_5$: MH^+: 677.8 Found: MH^+: 677.6;

4-[4-(3-piperid-4-ylpropylcarbamoyl)piperazin-1-ylcarbonyl]benzyl 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate (Compound 7); Calculated for $C_{35}H_{50}N_{10}O_5$: MH^+: 691.9 Found: MH^+: 691.5;

4-[4-(4-piperid-4-ylbutylcarbamoyl)piperazin-1-ylcarbonyl]benzyl 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate (Compound 8); Calculated for $C_{36}H_{52}N_{10}O_5$: MH^+: 705.9 Found: MH^+: 705.9;

4-[4-(4-guanidinobenzylcarbamoyl)piperazin-1-ylcarbonyl]benzyl 4-(2-piperid-4-ylethylcarbamoyl)-1-piperazinecarboxylate (Compound 9); Calculated for $C_{34}H_{48}N_{10}O_5$: MH^+: 677.8 Found: MH^+: 677.7;

4-[4-(4-guanidinobenzylcarbamoyl)piperazin-1-ylcarbonyl]benzyl 4-(3-piperid-4-ylpropylcarbamoyl)-1-piperazinecarboxylate (Compound 10); Calculated for $C_{35}H_{50}N_{10}O_5$: MH^+: 691.9 Found: MH^+: 691.3;

4-[4-(2-piperid-4-ylethylcarbamoyl)piperazin-1-ylcarbonylmethyl]benzyl 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate (Compound 11); Calculated for $C_{35}H_{50}N_{10}O_5$: MH^+: 691.9 Found: MH^+: 692.1;

4-[4-(3-piperid-4-ylpropylcarbamoyl)piperazin-1-ylcarbonylmethyl]benzyl 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate (Compound 12); Calculated for $C_{36}H_{52}N_{10}O_5$: MH^+: 705.9 Found: MH^+: 705.6;

cis-1,5-cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-(4-methylaminomethylbenzylcarbamoyl)-1-piperazinecarboxylate (Compound 13); Calculated for $C_{37}H_{54}N_{10}O_6$: MH^+: 735.9 Found: MH^+: 735.7;

cis-1,5-cyclooctylene 4-(4-guanidinophenylacetyl)-1-piperazinecarboxylate 4-(2-piperid-4-ylethylcarbamoyl)-1-piperazinecarboxylate (Compound 14); Calculated for $C_{35}H_{55}N_9O_6$: MH^+: 698.9, Found: MH^+: 698.2;

cis-1,5-cyclooctylene 4-(4-guanidinophenylacetyl)-1-piperazinecarboxylate

4-(3-piperid-4-ylpropylcarbamoyl)-1-piperazinecarboxylate (Compound 15); Calculated for $C_{36}H_{57}N_9O_6$: MH^+: 712.9, Found: MH^+: 712.3;

cis-1,5-cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-(4-imidazol-1-ylbutylcarbamoyl)-1-piperazinecarboxylate (Compound 16); Calculated for $C_{35}H_{53}N_{11}O_6$: MH^+: 724.9, Found: MH^+: 724.5;

cis-1,5-cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-(4-imidazolin-2-ylaminobutylcarbamoyl)-1-piperazinecarboxylate (Compound 17); Calculated for $C_{35}H_{56}N_{12}O_6$: MH^+: 741.9, Found: MH^+: 741.7;

cis-1,5-cyclooctylene 4-(*trans*-4-aminocyclohexylmethylcarbamoyl)-1-piperazinecarboxylate 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate (Compound 18); Calculated for $C_{35}H_{56}N_{10}O_6$: MH^+: 713.9 Found: MH^+: 714.1;

cis-1,5-cyclooctylene 2-(1-*tert*-butryryloxymethoxycarbonylpiperid-4-yl)ethylcarbamoyl-1-piperazinecarboxylate 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate (Compound 19); Calculated for $C_{42}H_{66}N_{10}O_{10}$: MH^+: 872.1, Found: MH^+: 871.8;

cis-1,5-cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-[2-(1-methylpiperid-4-yl)ethylcarbamoyl]-1-piperazinecarboxylate (Compound 20); Calculated for $C_{36}H_{58}N_{10}O_6$: $MH_2^{2+}/2$: 364.0, Found: $MH_2^{2+}/2$: 364.3;

cis-1,5-cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-(3-imidazolin-2-ylaminopropylcarbamoyl)-1-piperazinecarboxylate (Compound 21); Calculated for $C_{34}H_{54}N_{12}O_6$: MH^+: 727.9, Found: MH^+: 728.0;

cis-1,5-cyclooctylene 4-(4-guanidinophenylacetyl)-1-piperazinecarboxylate 4-[1-(1-iminoethyl)piperid-4-ylmethylcarbamoyl]-1-piperazinecarboxylate (Compound 22); Calculated for $C_{36}H_{57}N_{11}O_6$: MH^+: 740.9, Found: MH^+: 740.5;

cis-1,5-cyclooctylene 4-(4-guanidinobenzoylaminomethyl)-1-piperidinecarboxylate 4-(2-piperid-4-ylethylcarbamoyl)-1-piperazinecarboxylate (Compound 23); Calculated for $C_{36}H_{57}N_9O_6$: MH^+: 712.9, Found: MH^+: 711.6;

cis-1,5-cyclooctylene 4-(4-amidinobenzylcarbamoyl)-1-piperazinecarboxylate 2-(1-methoxycarbonylpiperid-4-yl)ethylcarbamoyl-1-piperazinecarboxylate (Compound 24); Calculated for $C_{37}H_{57}N_9O_8$: MH^+: 756.9, Found: MH^+: 756.7; and

3-{4-[2-(4-{*cis*-5-[4-(4-amidinobenzylcarbamoyl)piperazin-1-ylcarbonyloxy]cyclooctyloxy-carbonyl}piperazin-1-ylcarbonylamino)ethyl]piperid-1-ylcarbonyl}propionic acid (Compound 25); Calculated for $C_{39}H_{60}N_9O_9$: MH^+: 799.0, Found: MH^+: 798.6.

Proceeding as in Example 8 and replacing the isocyanate with an activated ester the following compounds of Formula I were prepared:

cis-1,5-cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-imidazol-4-ylacetyl-1-piperazinecarboxylate (Compound 26); Calculated for $C_{32}H_{46}N_{10}O_6$: MH^+: 667.8, Found: MH^+: 667.7;

cis-1,5-cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-(*E*-3-imidazol-4-ylacryloyl)-1-piperazinecarboxylate (Compound 27); Calculated for $C_{33}H_{46}N_{10}O_6$: MH^+: 679.9, Found: MH^+: 679.8;

cis-1,5-cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-(3-imidazol-4-ylpropionyl)-1-piperazinecarboxylate (Compound 28); Calculated for $C_{33}H_{48}N_{10}O_6$: MH^+: 681.8, Found: MH^+: 681.7;

cis-1,5-cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-(5-imidazol-1-ylvaleryl)-1-piperazinecarboxylate (Compound 29); Calculated for $C_{35}H_{52}N_{10}O_6$: MH^+: 709.9, Found: MH^+: 709.5;

cis-1,5-cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-(6-imidazol-1-ylhexanoyl)-1-piperazinecarboxylate (Compound 30); Calculated for $C_{36}H_{54}N_{10}O_6$: MH^+: 723.9, Found: MH^+: 723.4;

cis-1,5-cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-(4-imidazol-1-ylmethylphenylacetyl)-1-piperazinecarboxylate (Compound 31); Calculated for $C_{39}H_{52}N_{10}O_6$: MH^+: 757.9, Found: MH^+: 757.2;

cis-1,5-cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-(4-imidazol-1-ylmethylbenzoyl)-1-piperazinecarboxylate (Compound 32); Calculated for $C_{38}H_{50}N_{10}O_6$: MH^+: 743.9, Found: MH^+: 743.7;

cis-1,5-cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-(3-imidazol-1-ylmethylbenzoyl)-1-piperazinecarboxylate (Compound 33); Calculated for

$C_{38}H_{50}N_{10}O_6$: MH^+: 743.9, Found: MH^+: 743.6;

cis-1,5-cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-(7-imidazol-1-ylheptanoyl)-1-piperazinecarboxylate (Compound 34); Calculated for $C_{37}H_{56}N_{10}O_6$: MH^+: 737.9, Found: MH^+: 737.6;

cis-1,5-cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-[6-(2-methylimidazol-1-yl)hexanoyl]-1-piperazinecarboxylate (Compound 35); Calculated for $C_{37}H_{56}N_{10}O_6$: MH^+: 737.9, Found: MH^+: 737.3;

cis-1,5-cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-(4-imidazol-1-ylphenoxyacetyl)-1-piperazinecarboxylate (Compound 36); Calculated for $C_{38}H_{50}N_{10}O_7$: MH^+: 759.9, Found: MH^+: 759.3;

cis-1,5-cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-[6-(4-methylimidazol-1-yl)hexanoyl]-1-piperazinecarboxylate and *cis*-1,5-cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-[6-(5-methylimidazol-1-yl)hexanoyl]-1-piperazinecarboxylate as a mixture (Compound 37); Calculated for $C_{37}H_{56}N_{10}O_6$: MH^+: 737.9, Found: MH^+: 738.2;

cis-1,5-cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-(4-piperid-4-ylbutyryl)-1-piperazinecarboxylate (Compound 38); Calculated for $C_{36}H_{57}N_9O_6$: MH^+: 712.9 Found: MH^+: 712.4;

cis-1,5-cyclooctylene 4-(4-guanidinophenylacetyl)-1-piperazinecarboxylate 4-(4-piperid-4-ylbutyryl)-1-piperazinecarboxylate (Compound 39); Calculated for $C_{36}H_{56}N_8O_6$: MH^+: 697.9, Found: MH^+: 697.5;

cis-1,5-cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-(2-piperid-4-ylethyl)(methyl)carbamoyl-1-piperazinecarboxylate (Compound 40); Calculated for $C_{36}H_{58}N_{10}O_6$: MH^+: 727.9, Found: MH^+: 727.6;

cis-1,5-cyclooctylene 4-(4-guanidinophenylacetyl)-1-piperazinecarboxylate 4-(2-piperid-4-ylethyl)(methyl)carbamoyl-1-piperazinecarboxylate (Compound 41); Calculated for $C_{36}H_{57}N_9O_6$: MH^+: 712.9, Found: MH^+: 712.7;

cis-1,5-cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-(2-piperid-4-ylethoxycarbonyl)-1-piperazinecarboxylate (Compound 42); Calculated for $C_{35}H_{55}N_9O_7$: MH^+: 714.9, Found: MH^+: 714.5;

cis-1,5-cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-(4-imidazol-1-ylphenylacetyl)-1-piperazinecarboxylate (Compound 43); Calculated for $C_{38}H_{50}N_{10}O_6$: MH$^+$: 743.9, Found: MH$^+$: 743.6;

cis-1,5-cyclooctylene 4-(4-guanidinophenylacetyl)-1-piperazinecarboxylate 4-(6-imidazol-1-ylhexanoyl)-1-piperazinecarboxylate (Compound 44); Calculated for $C_{36}H_{53}N_9O_6$: MH$^+$: 708.9, Found: MH$^+$: 708.8;

cis-1,5-cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-(3-pyrid-4-ylthiopropionyl)-1-piperazinecarboxylate (Compound 45); Calculated for $C_{35}H_{49}N_9O_6$: MH$^+$: 724.9, Found: MH$^+$: 724.4;

cis-1,5-cyclooctylene 4-(4-guanidinobenzylcarbonyl)-1-piperazinecarboxylate 4-pyrid-4-ylthioacetyl-1-piperazinecarboxylate (Compound 46); Calculated for $C_{34}H_{47}N_9O_6$: MH$^+$: 710.9, Found: MH$^+$: 710.8;

cis-1,5-cyclooctylene 4-(4-guanidinophenylacetyl)-1-piperazinecarboxylate 4-(3-pyrid-4-ylthiopropionyl)-1-piperazinecarboxylate (Compound 47); Calculated for $C_{35}H_{48}N_8O_6$: MH$^+$: 709.9, Found: MH$^+$: 709.3;

cis-1,5-cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-(6-imidazol-4-ylhexanoyl)-1-piperazinecarboxylate (Compound 48); Calculated for $C_{36}H_{54}N_{10}O_6$: MH$^+$: 723.9, Found: MH$^+$: 723.5;

cis-1,5-cyclooctylene 4-(benzoimidazol-6-ylcarbonyl)-1-piperazinecarboxylate 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate (Compound 49); Calculated for $C_{35}H_{47}N_{10}O_6$: MH$^+$: 703.8, Found: MH$^+$: 703.4;

cis-1,5-cyclooctylene 4-(4-amidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-(6-imidazol-1-ylhexanoyl)-1-piperazinecarboxylate (Compound 50); Calculated for $C_{36}H_{53}N_9O_6$: MH$^+$: 708.9, Found: MH$^+$: 708.6;

cis-1,5-cyclooctylene 4-(4-amidinobenzoylaminomethyl)-1-piperidinecarboxylate 4-(6-imidazol-4-ylhexanoyl)-1-piperazinecarboxylate (Compound 51); Calculated for $C_{37}H_{54}N_8O_6$: MH$^+$: 707.9, Found: MH$^+$: 707.5;

cis-1,5-cyclooctylene 4-(4-guanidinophenylacetyl)-1-piperazinecarboxylate 4-(6-imidazol-4-ylhexanoyl)-1-piperazinecarboxylate (Compound 52); Calculated for $C_{35}H_{52}N_{10}O_6$: MH$^+$: 708.9 Found: MH$^+$: 708.4;

cis-1,5-cyclooctylene 4-(4-guanidinophenylacetyl)-1-piperazinecarboxylate 4-pyrid-4-ylcarbamoylacetyl-1-piperazinecarboxylate (Compound 53); Calculated for $C_{35}H_{47}N_9O_7$: MH^+: 706.8, Found: MH^+: 706.3;

cis-1,5-cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-(3-pyrid-4-ylaminopropionyl)-1-piperazinecarboxylate (Compound 54); Calculated for $C_{35}H_{50}N_{10}O_6$: MH^+: 707.9, Found: MH^+: 707.3;

cis-1,5-cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 3-[pyrid-4-yl(*tert*-butoxycarbonyl)amino]propionyl-1-piperazinecarboxylate (Compound 55); Calculated for $C_{40}H_{58}N_{10}O_8$: $MH_2^{2+}/2$: 404.5, Found: $MH_2^{2+}/2$: 404.2;

cis-1,5-cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-(3-piperazin-1-ylcarbonylpropionyl)-1-piperazinecarboxylate (Compound 56); Calculated for $C_{35}H_{54}N_{10}O_7$: MH^+: 727.9, Found: MH^+: 727.5;

cis-1,5-cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-piperid-1-ylcarbonylaminoacetyl-1-piperazinecarboxylate (Compound 57); Calculated for $C_{35}H_{54}N_{10}O_7$: MH^+: 727.9, Found: MH^+: 727.5;

cis-1,5-cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-(5-imidazol-4-ylvaleryl)-1-piperazinecarboxylate (Compound 58); Calculated for $C_{35}H_{52}N_{10}O_6$: MH^+: 708.9, Found: MH^+: 709.4;

cis-1,5-cyclooctylene 4-(4-amidinobenzoylaminomethyl)-1-piperidinecarboxylate 4-(3-piperazin-1-ylcarbonylpropionyl)-1-piperazinecarboxylate (Compound 59); Calculated for $C_{36}H_{54}N_8O_7$: MH^+: 711.9, Found: MH^+: 711.4;

cis-1,5-cyclooctylene 4-(4-amidinobenzoylaminomethyl)-1-piperidinecarboxylate 4-piperid-4-ylcarbonylaminoacetyl-1-piperazinecarboxylate (Compound 60); Calculated for $C_{36}H_{54}N_8O_7$: MH^+: 711.9, Found: MH^+: 711.4;

cis-1,5-cyclooctylene 4-[3-(2-aminopyrimidin-5-yl)propionyl]-1-piperazinecarboxylate 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate (Compound 61); Calculated for $C_{34}H_{49}N_{11}O_6$: MH^+: 708.8, Found: MH^+: 708.4;

cis-1,5-cyclooctylene 4-[3-(6-aminopyrid-3-yl)propionyl]-1-piperazinecarboxylate 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate (Compound 62); Calculated for $C_{35}H_{50}N_{10}O_6$: MH^+: 707.8, Found: MH^+: 707.4;

cis-1,5-cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-[4-(4-pyrid-4-ylthio)butyryl]-1-piperazinecarboxylate (Compound 63); Calculated for $C_{36}H_{51}N_9O_6$: MH$^+$: 738.9, Found: MH$^+$: 738.4;

cis-1,5-cyclooctylene 4-[3-(2-amino-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)propionyl]-1-piperazinecarboxylate 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate (Compound 64); Calculated for $C_{34}H_{48}N_{10}O_8$: MH$^+$: 725.8, Found: MH$^+$: 725.2;

cis-1,5-cyclooctylene 4-(4-amidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-(4-piperid-4-ylbutyryl)-1-piperazinecarboxylate (Compound 65); Calculated for $C_{36}H_{56}N_8O_6$: MH$^+$: 697.9, Found: MH$^+$: 697.4;

cis-1,5-cyclooctylene 4-(4-amidinobenzoylaminomethyl)-1-piperidinecarboxylate 4-(4-piperid-4-ylbutyryl)-1-piperazinecarboxylate (Compound 66); Calculated for $C_{37}H_{57}N_7O_6$: MH$^+$: 696.9, Found: MH$^+$: 696.4;

cis-1,5-cyclooctylene 4-(1-amidinopiperid-4-ylacetyl)-1-piperidinecarboxylate 4-(6-imidazol-1-ylhexanoyl)-1-piperazinecarboxylate (Compound 67); Calculated for $C_{35}H_{57}N_9O_6$: MH$^+$: 700.9, Found: MH$^+$: 700.5;

cis-1,5-cyclooctylene 4-(1-amidino-4-piperidylacetyl)-1-piperazinecarboxylate 4-(4-piperid-4-ylbutyryl)-1-piperazinecarboxylate (Compound 68); Calculated for $C_{35}H_{60}N_8O_6$: MH$^+$: 689.9, Found: MH$^+$: 689.4;

cis-1,5-cyclooctylene 4-(1-amidino-4-piperidylacetyl)-1-piperazinecarboxylate 4-(6-imidazol-1-ylhexanoyl)-1-piperazinecarboxylate (Compound 69); Calculated for $C_{35}H_{57}N_9O_6$: MH$^+$: 700.9, Found: MH$^+$: 700.4;

cis-1,5-cyclooctylene 4-(4-amidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-(6-imidazol-4-ylhexanoyl)-1-piperazinecarboxylate (Compound 70); Calculated for $C_{36}H_{53}N_9O_6$: MH$^+$: 708.9, Found: MH$^+$: 708.4;

cis-1,5-cyclooctylene 4-(4-amidinobenzoylaminomethyl)-1-piperidinecarboxylate 4-(6-imidazol-4-ylhexanoyl)-1-piperazinecarboxylate (Compound 71); Calculated for $C_{37}H_{54}N_8O_6$: MH$^+$: 707.9, Found: MH$^+$: 707.4;

cis-1,5-cyclooctylene 4-(4-amidinophenylacetyl)-1-piperazinecarboxylate 4-(6-imidazol-1-ylhexanoyl)-1-piperazinecarboxylate (Compound 72); Calculated for

$C_{36}H_{52}N_8O_6$: MH^+: 693.9, Found: MH^+: 693.4;

cis-1,5-cyclooctylene 4-(4-amidinophenylacetyl)-1-piperazinecarboxylate 4-(4-piperid-4-ylbutyryl)-1-piperazinecarboxylate (Compound 73); Calculated for $C_{36}H_{55}N_7O_6$: MH^+: 682.9, Found: MH^+: 682.4;

cis-1,5-cyclooctylene 4-(4-amidinophenylacetyl)-1-piperazinecarboxylate 4-(6-imidazol-4-ylhexanoyl)-1-piperazinecarboxylate (Compound 74); Calculated for $C_{36}H_{52}N_8O_6$: MH^+: 693.9 MH^+: 693.4; and

cis-1,5-cyclooctylene 4-(4-amidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-[4-(2-(1-*tert*-butylcarbonyloxymethoxycarbonyl)piperid-4-ylethylcarbamoyl)-1-piperazinecarboxylate (Compound 75); Calculated for $C_{42}H_{65}N_9O_{10}$: MH^+: 857.0 Found: MH^+: 856.6.

EXAMPLE 9

cis-1,5-cyclooctylene di(4-*tert*-butoxycarbonyl-1-piperazinecarboxylate)

cis-1,5-Cyclooctylene di(chloroformate) (3.69 g, 13.7 mmol.), prepared as in Example 5, and DIEA (7.2 mL, 41 mmol.) were taken into DMF (25 mL) and *tert*-butyl 1-piperazinecarboxylate (5.1 g, 27.4 mmol.) was added. The mixture was stirred 12 hours at room temperature and then concentrated *in vacuo* giving a semi-solid residue. The residue was partitioned between dichloromethane (50 mL) and water (50 mL) and the dichloromethane layer was washed with 0.1N aqueous hydrochloric acid (2x, 25 mL), dried ($MgSO_4$) and filtered. Concentrating *in vacuo* gave *cis*-1,5-cyclooctylene di(4-*tert*-butoxycarbonyl-1-piperazinecarboxylate) as an amorphous solid; ^{1}H-NMR (300MHz, $CDCl_3$): 4.80 (m, 2H), 3.40 (br s, 16H), 2.00-1.40 (m, 12H), 1.40 (s, 18H).

EXAMPLE 10

cis-1,5-cyclooctylene di[4-(2-piperid-4-ylethylcarbamoyl)-1-piperazinecarboxylate] (Compound 76)

The following is the preparation of a compound of Formula I in which R^1 and R^2 each are 2-piperid-4-ylethyl, X^1 and X^9 each are -NHC(O)-, X^2 and X^8 each are 1,4-piperazinylene, X^3 and X^7 each are -C(O)O-, X^4 and X^6 each are a covalent bond and X^5 is *cis*-1,5-cyclooctylene.

cis-1,5-Cyclooctylene di(4-*tert*-butoxycarbonyl-1-piperazinecarboxylate) (47.9 mg, 0.088 mmol.), prepared as Example 9, was treated with TFA (1 mL) neat for 10 minutes giving a colorless oil. The mixture was concentrated *in vacuo* and the residue was triturated with ethyl ether (2x, 5 mL) and repeatedly dried *in vacuo* giving an amorphous solid. The solid residue was taken into DMF (5 mL) and DIEA (100 mL, 0.5 mmol.) and then *tert*-butyl 4-(2-isocyanatoethyl)-1-piperidinecarboxylate (460 mL, 0.39 M in DMF, 0.18 mmol.) was added to the solution. The mixture was stirred 12 hours and concentrated *in vacuo*. The residue was triturated with water (2x, 5 mL) and dried *in vacuo* giving a yellow solid. The solid was treated with TFA (2 mL) and the mixture was concentrated *in vacuo*. The residue was taken into water. Purifying from the aqueous mixture by preparative reverse phase HPLC followed by

lyophillization gave *cis*-1,5-cyclooctylene di[4-(2-piperid-4-ylethylcarbamoyl)-1-piperazinecarboxylate] as a colorless amorphous solid; Electrospray LRMS: Calculated for $C_{34}H_{60}N_8O_6$: MH^+: 677.9, Found: MH^+: 677.6.

Proceeding as in Example 10 and substituting different starting materials *cis*-1,5-cyclooctylene di[4-(4-methylaminomethylbenzylcarbamoyl)-1-piperazinecarboxylate] (Compound 77) was prepared; Calculated for $C_{38}H_{56}N_8O_6$: MH^+: 721.9, Found: MH^+: 721.7.

Proceeding as in Example 10 and replacing the isocyanate with an activated ester the following compounds of Formula I were prepared:

cis-1,5-cyclooctylene di[4-(4-piperid-4-ylbutyryl)-1-piperazinecarboxylate] (Compound 78); Calculated for $C_{36}H_{62}N_6O_6$: MH^+: 675.9, Found: MH^+: 675.6; and *para*-dimethylenephenylene di[4-(4-piperid-4-ylbutyryl)-1-piperazinecarboxylate] (Compound 79); Calculated for $C_{36}H_{56}N_6O_6$: MH^+: 669.9, Found: MH^+: 669.4.

EXAMPLE 11

tert-Butyl 4-(3-imidazol-1-ylpropylcarbamoyl)-1-piperazinecarboxylate

tert-Butyl 4-chlorocarbonyl-1-piperazinecarboxylate (188 mg, 0.76 mmol.), prepared as in Example 3, was taken into dichloromethane (10 mL) and DIEA (150 mL, 0.86 mmol) was added. 1-(3-Aminopropyl)imidazole (100 mL, 0.84 mmol) was added by syringe and the mixture was stirred 12 hours. Dichloromethane (10 mL) was added to the mixture and the organic layer was washed with water (1x, 10 mL), dried ($MgSO_4$) and filtered. Concentrating gave *tert*-butyl 4-(3-imidazol-1-ylpropylcarbamoyl)-1-piperazinecarboxylate (230 mg, 0.68 mmol, 90% yield) as a colorless oil; ^{1}H-NMR (300MHz, DMSO-d_6): 7.60 (s, 1H), 7.20 (s, 1H), 6.85 (s, 1H), 6.60 (tr, 1H), 3.95 (tr, 2H), 3.30 (s, 8H), 3.00 (q, 2H), 1.80 (m, 2H), 1.40 (s, 9H).

EXAMPLE 12

tert-Butyl 4-aminomethyl-1-benzenecarbamate hydrochloride

4-Aminobenzylamine (5.56 g, 45.6 mmol.) was taken into water (45 mL) and citric acid (9.63 g, 50 mmol) was added to the solution. Di-*tert*-butyl dicarbonate (9.94 g, 45.5 mmol) in dioxane (20 mL) was added dropwise to the solution and the mixture was stirred 48 hours at room temperature giving a yellow suspension. The suspension was filtered and the aqueous solution was basified with excess solid sodium carbonate and extracted with ethyl acetate (3x, 35 mL). The combined extracts were washed with saturated aqueous sodium chloride, dried ($MgSO_4$), filtered and concentrated *in vacuo* giving a white solid. The solid was taken into methanol (30 mL), the solution was acidified with hydrogen chloride in dioxane (4M, 8.4 mL, 33.6 mmol.) and then ethyl ether (100 mL) was added giving a suspension. The particulate matter was isolated by filtration. Drying *in vacuo* gave *tert*-butyl 4-aminomethyl-1-benzenecarbamate hydrochloride (7.2 g, 27.8 mmol, 61% yield) as a colorless solid; ^{1}H-NMR (300MHz, DMSO-d_6): 9.43 (s, 1H), 8.20 (br s, 3H), 7.40 (dd AB, 4H), 3.92 (m, 2H), 1.50 (s, 9H).

EXAMPLE 13

tert-Butyl 4-isocyanatomethyl-1-benzenecarbamate:

tert-Butyl 4-aminomethyl-1-benzenecarbamate hydrochloride (3.39 g, 13.1 mmol), prepared as in Example 12, was taken into dichloromethane (120 mL) at 0°C and pyridine (4.3 mL, 53 mmol) and triphosgene (1.3 g, 4.4 mmol) was added. The mixture was allowed to warm to room temperature over 30 minutes and aqueous hydrochloric acid (0.5N, 100 mL) was added. The organic layer was dried ($MgSO_4$) and filtered. Concentrating gave *tert*-butyl 4-isocyanatomethyl-1-benzenecarbamate (2.7 g, 11 mmol, 84% yield) as a yellow solid; ^{1}H-NMR (300MHz, $CDCl_3$): 7.29 (dd AB, 4H), 6.55 (br s, 1H), 4.40 (s, 2H), 1.55 (s, 9H).

EXAMPLE 14

cis-1,5-Cyclooctylene 4-(4-aminobenzylcarbamoyl)-1-piperazinecarboxylate 4-(3-imidazol-1-ylpropylcarbamoyl)-1-piperazinecarboxylate (Compound 80)

The following is the preparation of a compound of Formula I in which R^1 is 4-aminobenzyl, R^2 is 3-imidazol-1-ylpropyl, X^1 and X^9 each are -NHC(O)-, X^2 and X^8 each are 1,4-piperazinylene, X^3 and X^7 each are -C(O)O-, X^4 and X^6 each are a covalent bond and X^5 is *cis*-1,5-cyclooctylene.

(a) *tert*-Butyl 4-(3-imidazol-1-ylpropylcarbamoyl)-1-piperazinecarboxylate (225 mg, 0.67 mmol), prepared as in Example 11, was treated with TFA (1 mL) neat for 10 minutes. The mixture was concentrated *in vacuo* and the residue was taken into dichloromethane (10 mL) and an excess of DIEA (1.0 mL) was added to the solution. *cis*-1,5-Cyclooctylene chloroformate 4-*tert*-butoxycarbonyl-1-piperazinecarboxylate (279 mg, 0.67 mmol), prepared as in Example 6, in dichloromethane (5 mL) was added to the solution and the mixture was stirred for 1 hour. Additional dichloromethane (10 mL) was added and the organic layer was washed with saturated aqueous sodium bicarbonate (1x, 10 mL), dried ($MgSO_4$) and filtered. Concentrating gave crude *cis*-1,5-cyclooctylene 4-(3-imidazol-1-ylpropylcarbamoyl)-1-piperazinecarboxylate *tert*-butoxycarbonyl-1-piperazinecarboxylate adduct as a colorless foam.

(b) The adduct prepared in Part (a) was treated with TFA (1 mL) neat for 10 minutes and then the mixture was concentrated *in vacuo*. The residue was taken into DMF (10 mL) and an excess of DIEA (1.5 mL) and *tert*-butyl 4-isocyanatomethyl-1-benzenecarbamate (165 mg, 0.67 mmol.), prepared as in Example 13 were added. The mixture was stirred 12 hours and concentrated *in vacuo*. The residue was treated with TFA neat and mixture was concentrated *in vacuo*. The residue was taken into water (15 mL) and the aqueous solution was extracted with ethyl ether (1x, 15 mL). The aqueous layer was basified with 1.0M aqueous sodium hydroxide and then extracted with dichloromethane. The dichloromethane was dried ($MgSO_4$) and filtered. Concentrating *in vacuo* gave *cis*-1,5-cyclooctylene 4-(4-aminobenzylcarbamoyl)-1-piperazinecarboxylate 4-(3-imidazol-1-ylpropylcarbamoyl)-1-piperazinecarboxylate as a colorless foam; ^{1}H-NMR (300MHz, $CDCl_3$): 7.45 (s, 1H), 7.10 (d, 2H), 7.05 (s, 1H), 6.90 (s,

1H), 6.60 (d, 2H), 4.85-4.70 (m, 4H), 4.30 (d, 2H), 4.00 (tr, 2H), 3.50-3.30 (m, 18H), 2.00 (m, 2H), 1.90-1.50 (m, 12H).

Proceeding as in Example 14 and substituting different starting materials the following compounds of Formula I were prepared:

cis-1,5-cyclooctylene 4-(4-aminobenzylcarbamoyl)-1-piperazinecarboxylate 4-(2-pyrid-4-ylethylcarbamoyl)-1-piperazinecarboxylate (Compound 81);

cis-1,5-cyclooctylene 4-(4-aminobenzylcarbamoyl)-1-piperazinecarboxylate 4-(3-piperid-4-ylpropyl)-1-piperidinecarboxylate (Compound 82); and

cis-1,5-cyclooctylene 4-(4-aminobenzylcarbamoyl)-1-piperazinecarboxylate 4-(4-piperid-4-ylbutyl)-1-piperidinecarboxylate (Compound 83).

EXAMPLE 15

cis-1,5-Cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-(3-imidazol-1-ylpropylcarbamoyl)-1-piperazinecarboxylate (Compound 84)

The following is the preparation of a compound of Formula I in which R^1 is 4-guanidinobenzyl, R^2 is 3-imidazol-1-ylpropyl, X^1 and X^9 each are -NHC(O)-, X^2 and X^8 each are 1,4-piperazinylene, X^3 and X^7 each are -C(O)O-, X^4 and X^6 each are a covalent bond and X^5 is *cis*-1,5-cyclooctylene.

cis-1,5-Cyclooctylene 4-(4-aminobenzylcarbamoyl)-1-piperazinecarboxylate 4-(3-imidazol-1-ylpropylcarbamoyl)-1-piperazinecarboxylate, prepared in Example 14, was taken into methanol and ethyl ether and an excess of hydrogen chloride (4M in dioxane) was added. The mixture was concentrated and dried *in vacuo*. An excess of cyanamide (1.0g) was added and the mixture was heated at 65°C for two hours giving a yellow solution. The mixture was allowed to cool to room temperatur and triturated with ethyl ether (3x, 10 mL). The insoluble residue was taken into water. Purifying from the aqueous mixture by preparative reverse phase HPLC gave *cis*-1,5-cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-

1-piperazinecarboxylate 4-(3-imidazol-1-ylpropylcarbamoyl)-1-piperazinecarboxylate as a colorless amorphous solid; Electrospray LRMS: Calculated for $C_{34}H_{51}N_{11}O_6$: MH^+: 710.9, Found: MH^+: 710.6.

Proceeding as in Example 15 and substituting different starting materials the following compounds of Formula I were prepared:

cis-1,5-cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-(2-pyrid-4-ylethylcarbamoyl)-1-piperazinecarboxylate (Compound 85); Calculated for $C_{35}H_{50}N_{10}O_6$: MH^+: 707.9 Found: MH^+: 707.6;

cis-1,5-cyclooctylene 3-piperid-4-ylpropyl-1-piperidinecarboxylate 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate (Compound 86); and

cis-1,5-cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-piperid-4-ylbutyl-1-piperidinecarboxylate (Compound 87); Calculated for $C_{37}H_{60}N_8O_5$: MH^+: 697.9, Found: MH^+: 697.7.

EXAMPLE 16

cis-1,5-cyclooctylene chloroformate 4-benzyloxycarbonyl-1-piperazinecarboxylate

Benzyl 1-piperazinecarboxylate (1.0 g, 4.53 mmol, 1.0 equiv) and DIEA (0.88 mL, 4.98 mmol, 1.1 equiv) in dichloromethane (25 mL) was added dropwise to *cis*-1,5-cyclooctylene di(chloroformate) (1.2 g, 4.53 mmol, 1.0 equiv), prepared as in Example 5, in dichloromethane (25 mL) at 0°C. The reaction mixture was stirred for 22 hours while allowing to warm to room temperature. The mixture was partitioned between dichloromethane, 0.05N aqueous hydrochloric acid and saturated aqueous sodium chloride. The organic layer was dried (Na_2SO_4) over sodium sulfate and concentrated. Purifying the residue by flash column chromatography, eluting with 20 and 30% ethyl acetate in hexanes, gave *cis*-1,5-cyclooctylene chloroformate 4-benzyloxycarbonyl-1-piperazinecarboxylate (0.81 g, 1.81 mmol, 40%) as a yellow oil; IR: 2939 (s), 2863 (m), 1770 (s), 1732 (s), 1696 (s); ^1H NMR (300 MHz, $CDCl_3$): 7.35 (s, 5 H), 5.15 (s, 2 H), 4.95 (m, 1 H), 4.75 (m, 1 H), 3.45 (s, 8 H), 1.50 – 2.05 (m, 12 H).

EXAMPLE 17

1-[*cis*-5-(4-Benzyloxycarbonylpiperazin-1-ylcarbonyloxy)cyclooctyloxycarbonyl]-4-piperidinecarboxylic acid

Isonipecotic acid (75 mg, 0.58 mmol, 1.1 equiv) and DIEA (0.23 mL, 1.33 mmol, 2.5 equiv) were added to *cis*-1,5-cyclooctylene chloroformate 4-benzyloxycarbonyl-1-piperazinecarboxylate (0.24 g, 0.53 mmol, 1.0 equiv), prepared as in Example 16, in dichloromethane (10 mL) at 0°C giving a white suspension. The suspension was stirred for 18 hours while allowing to warm to room temperature. The reaction mixture was partitioned between dichloromethane and 0.05N aqueous hydrochloric acid. Concentrating the organic layer gave crude 1-[*cis*-5-(4-benzyloxycarbonylpiperazin-1-ylcarbonyloxy)cyclooctyloxycarbonyl]-4-piperidinecarboxylic acid (0.36 g) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): 7.35 (s, 5 H), 5.15 (s, 2 H), 4.75 (m, 2 H), 3.90 (m, 1 H), 3.45 (s, 8 H), 2.75 (m, 1 H), 2.50 (m, 3 H), 1.50-1.90 (m, 16 H).

EXAMPLE 18

cis-1,5-Cyclooctylene 4-benzyloxycarbonyl-1-piperazinecarboxylate 4-[2-(1-*tert*-butoxycarbonylpiperid-4-yl)ethylcarbamoyl]-1-piperidinecarboxylate

1-Hydroxybenzotriazole hydrate (80 mg, 58.3 mmol, 1.1 equiv), *tert*-butyl 4-(2-aminoethyl)-1-piperidinecarboxylate hydrochloride (0.14 g, 0.53 mmol, 1.0 equiv) and 4-methylmorpholine (0.15 mL, 1.33 mmol, 2.5 equiv) were added to a solution of crude 1-[*cis*-5-(4-benzyloxycarbonylpiperazin-1-ylcarbonyloxy)cyclooctyloxycarbonyl]-4-piperidinecarboxylic acid (0.36 g, 0.53 mol, 1.0 equiv), prepared as in Example 17, in DMF (5 mL). 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.13 g, 0.66 mmol, 1.25 equiv) was added to the reaction mixture at 0 °C. The solution was stirred for 1.5 hours at 0°C and for 3 days at 23°C. The reaction mixture was partitioned between dichloromethane, 0.05N aqueous hydrochloric acid, saturated aqueous sodium bicarbonate, water (two portions) and saturated aqueous sodium chloride. The organic layer was dried (Na_2SO_4) and concentrated. Purifying from the residue by flash column chromat graphy, eluting with 3% methanol in

dichloromethane, gave *cis*-1,5-cyclooctylene 4-benzyloxycarbonyl-1-piperazinecarboxylate 4-[2-(1-*tert*-butoxycarbonylpiperid-4-yl)ethylcarbamoyl]-1-piperidinecarboxylate (0.15 g, 0.2 mmol, 37% over two steps) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): 7.35 (s, 5 H), 5.15 (s, 2 H), 4.80 (m, 2 H), 4.10 (m, 4 H), 3.45 (m, 10 H), 3.30 (m, 2 H), 2.70 (m, 2 H), 1.50-1.90 (m, 23 H), 1.45 (s, 9 H); Electrospray LRMS: calcd for $C_{40}H_{62}N_5O_9$ (MH^+): 756.97, obtained: 757.0.

EXAMPLE 19

cis-1,5-Cyclooctylene 1-piperazinecarboxylate 4-[2-(1-*tert*-butoxycarbonylpiperid-4-yl)ethylcarbamoyl]-1-piperidinecarboxylate

Ethanol (3 mL) was added to *cis*-1,5-cyclooctylene 4-benzyloxycarbonyl-1-piperazinecarboxylate 4-[2-(1-*tert*-butoxycarbonylpiperid-4-yl)ethylcarbamoyl]-1-piperidinecarboxylate (0.15 g, 0.20 mmol, 1.0 equiv), prepared as in Example 18, and 5% palladium on carbon (75 mg, 0.50 wt equiv) under nitrogen. The mixture was stirred under hydrogen (1 atm) for 17 hours at 23 °C. The reaction mixture was placed under nitrogen and filtered. Concentrating the filtrate gave *cis*-1,5-cyclooctylene 1-piperazinecarboxylate 4-[2-(1-*tert*-butoxycarbonylpiperid-4-yl)ethylcarbamoyl]-1-piperidinecarboxylate (110 mg, 0.18 mmol, 90%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): 5.5 (m, 1 H), 4.9 (m, 2 H), 4.75 (m, 1 H), 4.1 (m, 4 H), 3.45 (m, 4 H), 3.25 (m, 2 H), 2.60-2.85 (m, 8 H), 2.10 (m, 1 H), 1.50-1.95 (m, 23 H), 1.45 (s, 9 H); Electrospray LRMS: calcd for $C_{32}H_{56}N_5O_7$ (MH^+): 622.83, obtained: 622.7.

EXAMPLE 20

cis-1,5-Cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-(2-piperid-4-ylethylcarbamoyl)-1-piperidinecarboxylate (Compound 88)

The following is the preparation of a compound of Formula I in which R^1 is 4-guanidinobenzyl, R^2 is 2-piperid-4-ylethyl, X^1 and X^9 each are -NHC(O)-, X^2 is 1,4-piperazinylene, X^8 is 4,1-piperidylene, X^3 and X^7 each are -C(O)O-, X^4 and X^6 each are a covalent bond and X^5 is *cis*-1,5-cyclooctylene.

Triphosgene (30 mg, 0.10 mmol, 0.58 equiv) and pyridine (30 mL, 0.39 mmol, 2.1 equiv) were added to *cis*-1,5-cyclooctylene 1-piperazinecarboxylate 4-[2-(1-*tert*-butoxycarbonylpiperid-4-yl)ethylcarbamoyl]-1-piperidinecarboxylate (0.11 g, 0.18 mmol, 1.0 equiv), prepared as in Example 19, in dichloromethane (2 mL) at 0°C. The reaction mixture was stirred 3 hours at 0°C. The mixture was partitioned between dichloromethane, 0.05N aqueous hydrochloric acid and saturated aqueous sodium chloride. The organic layer was dried (Na_2SO_4) and concentrated giving a brown oil residue. 4-Guanidinobenzylamine dihydrochloride (43 mg, 0.20 mmol, 1.1 equiv) and DIEA (0.16 mL, 0.90 mmol, 5.0 equiv) in DMF (2 mL) were added to the residue giving a suspension. The suspension was stirred 18.5 hours at 23°C and concentrated. The residue was taken into 50% TFA in dichloromethane (4 mL) and the mixture was stirred 45 minutes at 23°C. The reaction mixture was concentrated and the residue was triturated with ether and dried *in vacuo*. Purifying from the residue by preparative reverse phase HPLC and lyophillization gave *cis*-1,5-cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-(2-piperid-4-ylethylcarbamoyl)-1-piperidinecarboxylate as a colorless amorphous solid; Electrospray LRMS: calcd for $C_{36}H_{58}N_9O_6$ (MH^+): 712.91, obtained: 712.8

Proceeding as in Example 20 and substituting different starting materials the following compounds of Formula I were prepared:

cis-1,5-cyclooctylene 4-(4-guanidinophenylacetyl)-1-piperazinecarboxylate

4-(3-imidazol-4-ylpropylcarbamoyl)-1-piperazinecarboxylate (Compound 89); Calculated for $C_{34}H_{50}N_{10}O_6$: MH^+: 695.9, Found: MH^+: 695.4;

cis-1,5-cyclooctylene 4-(4-guanidinophenylacetyl)-1-piperazinecarboxylate 4-(2-imidazol-4-ylethylcarbamoyl)-1-piperazinecarboxylate (Compound 90); Calculated for $C_{33}H_{48}N_{10}O_6$: MH^+: 681.3, Found: MH^+: 680.9;

cis-1,5-cyclooctylene 4-(4-guanidinophenylacetyl)-1-piperazinecarboxylate 4-(3-imidazol-1-ylpropylcarbamoyl)-1-piperazinecarboxylate (Compound 91); Calculated for $C_{34}H_{50}N_{10}O_6$: MH^+: 695.9, Found: MH^+: 694.9;

cis-1,5-cyclooctylene 4-(4-guanidinophenylacetyl)-1-piperazinecarboxylate 4-(4-imidazol-1-ylbutylcarbamoyl)-1-piperazinecarboxylate (Compound 92); Calculated for $C_{35}H_{53}N_{10}O_6$: MH^+: 709.9, Found: MH^+: 709.4; and

cis-1,5-cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-(3-imidazol-1-ylpropylcarbamoyl)-1-piperazinecarboxylate (Compound 93); Calculated for $C_{35}H_{51}N_{10}O_6$: MH^+: 709.9, Found: MH^+: 710.4.

EXAMPLE 21

3-Piperid-4-ylpropionic acid hydrochloride

4-Pyridineacrylic acid hydrochloride (12.0 g; 64.6 mmol) and 1.37 g of platinum oxide was suspended in acetic acid (80 mL) and hydrogenated 12 hours at 50 to 60 psi. The mixture was diluted with water and filtered through a pad of celite. The solids were washed with water (200 mL) and the combined filtrate and washings were concentrated *in vacuo* giving a white solid. The solid was suspended in a small amount of methanol and the mixture was diluted with diethyl ether (200 mL). The particulate matter was isolated by filtration and washed with diethyl ether and hexane. Air-drying gave 3-piperid-4-ylpropionic acid hydrochloride (11.3 g; 58.1 mmol, 90%) as a colorless solid; ^{1}H-NMR (300 MHz; DMSO-d_6): 8.75 (br s, 2H), 3.15 (d, 2H), 2.75 (t, 2H) 2.2 (t, 2H), 1.75 (d, 2H), 1.45 (t, 2H), 1.25 (br q, 2H).

EXAMPLE 22

3-(1-*tert*-Butyoxycarbonylpiperid-4-yl)propionic acid

3-Piperid-4-ylpropionic acid (5.07 g; 26.2 mmol), prepared as in Example 21, was dissolved in 2N aqueous NaOH (40 mL; 80 mmol). THF (40 mL) and then di(*tert*-butyl)dicarbonate (6.21 g; 28.4 mmol) was added giving a suspension. The suspension was stirred 22 hours, diluted with water and concentrated *in vacuo*. The residue was washed with diethyl ether (2x, 100 mL) and the aqueous phase was acidified to pH 2-3 with 1.0N aqueous $KHSO_4$ and extracted with ethyl acetate (3x, 200 mL). The combined organic phases were washed with brine and dried (Na_2SO_4). Concentrating *in vacuo* gave 3-[4-(1-*tert*-butoxycarbonyl)-4-piperidyl]propionic acid (6.21 g; 24.1 mmol, 92%) as a colorless oil that crystallized on standing; ^{1}H-NMR (300 MHz, $CDCl_3$): 4.10 (br d, 2H), 2.65 (br t, 2H), 2.35 (t, 2H), 1.70-1.50 (m, 3H), 1.45 (s, 9H), 1.20-0.95 (m, 2H).

EXAMPLE 23

tert-Butyl 4-benzyloxycarbonyl-1-piperazinecarboxylate

tert-Butyl 1-piperazinecarboxylate (2.01 g; 10.8 mmol) and DIEA (2.0 mL; 1.48 g; 11.5 mmol) in 50 mL of ice cold dichloromethane was treated with benzyl chloroformate (2.0 mL; 2.39 g; 14.0 mmol). The mixture was stirred for 42 hours and then partitioned between ethyl acetate and 0.5N $KHSO_4$. The aqueous phase was extracted with ethyl acetate and the combined organic layers were washed with water and brine, dried ($MgSO_4$) and concentrated. Purifying from the residue by chromatography over silica gel (ethyl acetate:hexane, 1:3) gave *tert*-butyl 4-benzyloxycarbonyl-1-piperazinecarboxylate (3.33 g; 10.4 mmol, 96%) as a colorless solid; ^{1}H-NMR (300 MHz, $CDCl_3$): 7.35 (br s, 5H), 5.13 (s, 2H), 3.55-3.25 (m, 8H), 1.45 (s, 9H).

EXAMPLE 24

Benzyl 1-piperazinecarboxylate hydrochloride

tert-Butyl 4-benzyloxycarbonyl-1-piperazinecarboxylate (1.01g; 3.16 mmol), prepared as in Example 23, was suspended in 4 mL of ethyl acetate. The suspension was cooled in an ice water bath and 4N hydrogen chloride (12 mL in 1,4-dioxane) was added giving a solution. The solution was stirred for 30 minutes on the ice bath and then for 30 minutes at room temperature. The reaction mixture was diluted with diethyl ether (75 mL) giving a precipitate. The precipitate was isolated by filtration and washed with diethyl ether. Drying *in vacuo* gave benzyl 1-piperazinecarboxylate hydrochloride (740 mg; 2.78 mmol, 88%) as a colorless solid; ^{1}H-NMR (300 MHz, DMSO-d_6): 9.25 (br s, 2H), 7.33 (s, 5H), 5.06 (s, 2H), 3.58 (br s, 4H), 3.04 (t, 4H).

EXAMPLE 25

tert-Butyl 4-[2-(4-benzyloxycarbonylpiperazin-1-ylcarbonylamino)ethyl]-1-piperidinecarboxylate

3-[4-(1-*tert*-Butoxycarbonyl)-4-piperidyl]propionic acid (2.16 g; 8.4 mmol), prepared as in Example 22, in dry benzene (28 mL) was treated with triethylamine (1.35 mL; 951 mg; 9.40 mmol) and diphenylphosphoryl azide (2.05 mL; 2.62 g; 9.53 mmol). The reaction mixture was gradually heated to reflux and kept at reflux for 3.5 hours. The mixture was cooled to room temperature then added dropwise to a suspension of benzyl 1-piperazinecarboxylate hydrochloride (2.44 g; 9.19 mmol), prepared as in Example 24, and triethylamine (1.40 mL; 1.02g; 10.0 mmol) in dry dichloromethane (10 mL). The reaction mixture was stirred for 43 hours and diluted with ethyl acetate and 0.5N $KHSO_4$. The organic layer was washed with water, aqueous sodium bicarbonate and brine, dried (Na_2SO_4) and concentrated. Purifying from the residue by chromatography on silica gel (ethyl acetate-hexane, 4:1; then pure ethyl acetate) gave *tert*-butyl 4-[2-(4-benzyloxycarbonylpiperazin-1-ylcarbonylamino)ethyl]-1-piperidinecarboxylate (3.84 g; 8.1 mmol, 96%) as a white solid; ^{1}H-NMR (300 MHz, $CDCl_3$): 7.35 (s, 5H), 5.15 (s, 2H), 4.50 (br t, 1H), 4.05 (br s, 2H), 3.55-3.45 (m, 4H), 3.40-3.30 (m, 4H), 3.25 (q, 2H), 2.65 (t, 2H), 1.70 (s, 2H), 1.45 (s, 11H), 1.20-1.00 (m, 2H).

EXAMPLE 26

cis-1,5-Cyclooctylene chloroformate 4-[2-(4-*tert*-butoxycarbonylpiperidin-4-yl)ethylcarbamoyl]-1-piperazinecarboxylate

tert-Butyl 4-[2-(4-benzyloxycarbonylpiperazin-1-ylcarbonylamino)ethyl]-1-piperidinecarboxylate (2.03 g; 4.28 mmol), prepared as in Example 25, and 10% palladium-on-carbon (570 mg) suspended in ethanol (19 mL) was hydrogenated at atmospheric pressure overnight. The reaction mixture was filtered and the catalyst was washed with ethanol. The filtrate and washings were concentrated *in vacuo* and the residue was dissolved in dichloromethane (30 mL) and treated with DIEA (500 mL). The solution was added dropwise to *cis*-1,5-cyclooctylene di(chloroformate) (4.15g; 15.4 mmol), prepared as in Example 5, in ice cold dichloromethane (75 mL). The reaction mixture was stirred overnight and diluted with 0.5N aqueous $KHSO_4$ and dichloromethane. The aqueous phase was extracted with dichloromethane and the combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. Purifying from the residue by chromatography on silica gel (ethyl acetate-hexane, 3:1; then pure ethyl acetate) gave *cis*-1,5-cyclooctylene chloroformate 4-[2-(4-*tert*-butoxycarbonylpiperidin-4-yl)ethylcarbamoyl]-1-piperazinecarboxylate (1.02 g; 1.8 mmol, 42%) as a pale yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): 5.00-4.90 (m, 1H), 4.85-4.75 (m, 1H), 4.35 (br t, 1H), 4.05 (br d, 2H), 3.50-3.40 (m, 4H), 3.35-3.30 (m, 4H), 3.25 (q, 2H), 2.65 (t, 2H), 2.05-1.55 (m, 17H), 1.40 (s, 9H), 1.25-1.00 (m, 2H).

EXAMPLE 27

4-Cyanophenylacetic acid

2-(4-Cyanophenyl)ethanol (5.00 g; 34.0 mmol) was dissolved in acetone (140 mL) and cooled to 10-15°C. A solution of CrO_3 in aqueous H_2SO_4 was added dropwise, while keeping the internal temperature below 30°C, until an orange color persisted giving a suspension. The suspension was stirred for 45 minutes and filtered. The solids were washed with acetone (150 mL) and the combined filtrate and washings were stirred with 2-propanol (20 mL) for 30 minutes. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was

taken intoethyl acetate and the solution was washed with 0.5N aqueous $KHSO_4$, water and brine and concentrated. The residue was dissolved in dichloromethane and the solution was treated with sodium hydroxide (1.56 g) in water (100 mL). The aqueous phase was extracted with dichloromethane and acidified to pH 1-2 with concentrated aqueous hydrochloric acid giving a precipitate. The precipitate was washed with water and air-dried. Drying *in vacuo* gave 4-cyanophenylacetic acid (3.36 g; 20.7 mmol, 61%) as a white powder; ^{1}H-NMR (300 MHz, $CDCl_3$): 7.63 (d, 2H), 7.40 (d, 2H), 3.72 (s, 2H).

EXAMPLE 28

tert-Butyl 4-(4-cyanophenylacetyl)-1-piperazinecarboxylate

A mixture of 4-cyanophenylacetic acid (890 mg; 5.52 mmol), prepared as in Example 27, ethylene dichloride (1.16 g; 6.07 mmol) and 1-hydroxybenzotriazole hydrate (820 mg; 6.07 mmol) was suspended in THF (18 mL) and *tert*-butyl 1-piperazinecarboxylate (1.04 g; 5.60 mmol) and DIEA were added to give a homogenous solution. The solution was concentrated *in vacuo* and the residue was treated with 0.2N $KHSO_4$. The mixture was filtered and the solid collected was washed with water. Drying *in vacuo* gave *tert*-butyl 4-(4-cyanophenylacetyl)-1-piperazinecarboxylate (1.68 g; 5.1 mmol, 92%) as a solid; ^{1}H-NMR (300 MHz, $CDCl_3$): 7.70 (d, 2H), 7.35 (d, 2H), 3.80 (s, 2H), 3.70-3.60 (m, 2H), 3.45-3.30 (m, 6H), 1.40 (s, 9H).

EXAMPLE 29

tert-Butyl 4-[4-(*N*-hydroxyamidino)phenylacetyl]-1-piperazinecarboxylate

tert-Butyl 4-(4-cyanophenylacetyl)-1-piperazinecarboxylate (1.68 g; 5.1 mmol), prepared as in Example 28, in dry ethanol (10 mL) was treated with hydroxylamine hydrochloride (461 mg; 6.63 mmol) and triethylamine (924 mL, 671 mg; 6.63 mmol). The mixture was heated at reflux for 3.5 hours, cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in ethanol, filtered and the filtrate cooled overnight giving a crystalline product. The crystals were isolated by filteration and washed with cold ethanol. Air-drying gave *tert*-butyl 4-[4-(*N*-hydroxyamidino)phenylacetyl]-1-piperazinecarboxylate (1.62 g; 4.5 mmol, 88%);

^{1}H-NMR (300 MHz, DMSO-d_6): 9.60 (s, 1H) 7.60 (d, 2H), 7.20 (d, 2H), 5.75 (s, 2H), 3.70 (s, 2H), 3.40 (br s, 4H), 3.25 (br s, 4H), 1.40 (s, 9H).

EXAMPLE 30

4-piperazin-1-ylcarbonylmethylbenzamidine bis(trifluoroacetate)

tert-Butyl 4-[4-(*N*-hydroxyamidino)phenylacetyl]-1-piperazinecarboxylate (653 mg; 1.81 mmol), prepared as in Example 29, and 10% palladium-on-carbon (200 mg) were suspended in acetic acid (12 mL) and hydrogen was bubbled through the suspension overnight. The reaction mixture was filtered and the catalyst was washed with acetic acid. The combined filtrate and washings were concentrated *in vacuo* and the residue was dissolved in TFA. The solution stood for 1 hour and then was concentrated *in vacuo*. The residue was co-evaporated from a mixture of dichloromethane and methanol and then suspended in diethyl ether. The particulate matter was collected by filtration. Drying gave 4-piperazin-1-ylcarbonylmethylbenzamidine bis(trifluoroacetate) (1.04 g; 1.81 mmol, 100%) as a white solid; ^{1}H-NMR (300 MHz, DMSO-d_6): 9.30 (d, 4H), 9.15 (br s, 2H), 7.70 (d, 2H), 7.40 (d, 2H), 3.85 (s, 2H), 3.65 (br d, 4H), 4.20-3.90 (m, 4H).

EXAMPLE 31

cis-1,5-Cyclooctylene 4-(4-amidinophenylacetyl)-1-piperazinecarboxylate
4-(2-piperid-4-ylethylcarbamoyl)-1-piperazinecarboxylate
(Compound 94)

The following is the preparation of a compound of Formula I in which R^1 is 4-amidinobenzyl, R^2 is 2-piperid-4-ylethyl, X^1 is -C(O)- and X^9 is -NHC(O)-, X^2 and X^8 each are 1,4-piperazinylene, X^3 and X^7 each are -C(O)O-, X^4 and X^6 each are a covalent bond and X^5 is *cis*-1,5-cyclooctylene.

4-Piperazin-1-ylcarbonylmethylbenzamidine bis(trifluoroacetate) (80 mg; 0.17 mmol), prepared as in Example 30, was dissolved in DMF (1.0 mL) and the solution was treated with DIEA (150 mL). *cis*-1,5-Cyclooctylene chloroformate 4-[2-(4-*tert*-butoxycarbonylpiperazin-1-yl)ethylcarbamoyl]-1-piperazinecarboxylate (100 mg), prepared as in Example 26, in DMF (1.0 mL) was added and the mixture was stirred overnight and concentrated *in vacuo*. The residue was dissolved in dichloromethane and TFA (1:1) and the mixture was concentrated *in vacuo*. The residue was triturated with diethyl ether giving a foam residue. Purifying from the residue by preparative reverse phase HPLC and lyophilization of the pure fractions gave *cis*-1,5-cyclooctylene 4-(4-amidinophenylacetyl)-1-piperazinecarboxylate 4-(2-piperid-4-ylethylcarbamoyl)-1-piperazinecarboxylate as a colorless solid; Electrospray LRMS: Calculated for $C_{35}H_{54}N_8O_8$: MH^+: 683.9; $MH_2^{+2}/2$: 342.5,, Found: MH^+: 683.8; $MH_2^{+2}/2$: 342.3.

Proceeding as in Example 31 and substituting different starting materials the following compounds of Formula I were prepared:

cis-1,5-cyclooctylene 4-(1-amidinopiperid-4-ylacetyl)-1-piperazinecarboxylate 4-(2-piperid-4-ylethylcarbamoyl)-1-piperazinecarboxylate (Compound 95); Calculated for $C_{34}H_{59}N_9O_6$: MH^+: 690.9, Found: MH^+: 690.6;

cis-1,5-cyclooctylene 4-(4-amidinobenzoylaminomethyl)-1-piperidinecarboxylate 4-(2-piperid-4-ylethylcarbamoyl)-1-piperazinecarboxylate (Compound 96); Calculated for

$C_{36}H_{56}N_8O_6$: MH^+: 697.9, Found: MH^+: 697.7;

cis-1,5-cyclooctylene 4-(4-amidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-(2-piperid-4-yl)ethylcarbamoyl]-1-piperazinecarboxylate (Compound 97); Calculated for $C_{35}H_{55}N_9O_6$: MH^+: 698.9, Found: MH^+: 698.7;

cis-1,5-cyclooctylene 4-(4-amidinophenylsulfonylaminomethyl)-1-piperidinecarboxylate 4-(2-piperid-4-ylethylcarbamoyl)-1-piperazinecarboxylate (Compound 98); Calculated for $C_{35}H_{56}N_8O_7$: MH^+: 733.9, Found: MH^+: 733.4;

cis-1,5-cyclooctylene 4-[2-(1-amidinopiperid-4-yl)ethylcarbamoyl]-1-piperazinecarboxylate 4-(2-piperid-4-ylethylcarbamoyl)-1-piperazinecarboxylate (Compound 99); Calculated for $C_{35}H_{62}N_{10}O_6$: MH^+: 719.9, Found: MH^+: 719.5;

cis-1,5-cyclooctylene 4-(4-amidinophenylcarbamoylmethyl)-1-piperidinecarboxylate 4-(2-piperid-4-ylethylcarbamoyl)-1-piperazinecarboxylate (Compound 100); Calculated for $C_{36}H_{56}N_8O_6$: MH^+: 697.9, Found: MH^+: 695.6;

cis-1,5-cyclooctylene 4-(4-*N*-methoxycarbonylamidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-(2-piperid-4-ylethylcarbamoyl)-1-piperazinecarboxylate (Compound 101); Calculated for $C_{37}H_{57}N_9O_8$: MH^+: 756.9, Found: MH^+: 756.4; and

cis-1,5-cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 3-piperid-4-ylpropyl-1-piperidinecarboxylate (Compound 102); Calculated for $C_{36}H_{58}N_8O_5$: MH^+: 683.9 Found: MH^+: 683.3.

EXAMPLE 32

1,5-Pentamethylene di[4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate] (Compound 103)

The following is the preparation of a compound of Formula I in which R^1 and R^2 each are 4-guanidinobenzyl, X^1 and X^9 each are -NHC(O)-, X^2 and X^8 each are 1,4-piperazinylene, X^3 and X^7 each are -C(O)O- and X^4-X^6-X^5 together are 1,5-pentamethylene.

tert-Butyl 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate trifluoroacetate (306 mg, 0.62 mmol.) was treated with neat trifluoroacetic acid (1mL) at room temperature over ten minutes to give a colorless homogeneous solution. The liquid was concentrated and the oily

residue triturated with diethyl ether (3x 10mL) followed by drying *in vacuo* to a colorless foam. The deprotected piperazine salt was then taken into DMF (2.5 mL) followed by addition of diisopropylethylamine (0.5 mL, 3.1 mmol.) and 1,5-n-pentylene di(chloroformate) (70 mg, 0.31 mmol.) and the mixture was allowed to stir for one hour at room temperature. The reaction mixture was concentrated and the residue was triturated with diethyl ether (3x 10mL) followed by drying *in vacuo*. The crude material was taken into water (5 mL) and purified by preparative reverse phase HPLC and lyophilization to give 1,5-n-pentylene di[4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate] as a colorless amorphous solid; Electrospray LRMS: Calculated for $C_{33}H_{48}N_{12}O_6$: MH^+: 709.8,, Found: MH^+: 709.3.

Proceeding as in Example 32 and substituting different starting materials the following compounds of formula I were prepared:

1,4-tetramethylene di[4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate] (Compound 104); Calculated for $C_{32}H_{46}N_{12}O_6$: MH^+: 695.8, Found: MH^+: 695.8;

4-guanidinobenzyl 4-{5-[4-(4-guanidinobenzylcarbamoyl)piperazin-1-ylcarbonyl]valeryl}-1-piperazinecarboxamide (Compound 105); Calculated for $C_{32}H_{46}N_{12}O_4$: MH^+: 663.8, Found: MH^+: 663.4;

4-guanidinobenzyl 4-{6-[4-(4-guanidinobenzylcarbamoyl)piperazin-1-ylcarbonyl]hexanoyl}-1-piperazinecarboxamide (Compound 106); Calculated for $C_{33}H_{48}N_{12}O_4$: MH^+: 677.8, Found: MH^+: 677.4;

4-guanidinobenzyl 4-{7-[4-(4-guanidinobenzylcarbamoyl)piperazin-1-ylcarbonyl]heptanoyl}-1-piperazinecarboxamide (Compound 107); Calculated for $C_{34}H_{50}N_{12}O_4$: MH^+: 691.9, Found: MH^+: 691.5;

4-guanidinobenzyl 4-{8-[4-(4-guanidinobenzylcarbamoyl)piperazin-1-ylcarbonyl]octanoyl}-1-piperazinecarboxamide (Compound 108); Calculated for $C_{37}H_{57}N_9O_8$: MH^+: 756.9, Found: MH^+: 756.4;

4-guanidinobenzyl 4-{9-[4-(4-guanidinobenzylcarbamoyl)piperazin-1-ylcarbonyl]nonanoyl}-1-piperazinecarboxamide (Compound 109); Calculated for $C_{36}H_{54}N_{12}O_4$: MH^+: 719.9, Found: MH^+: 719.5;

4-amidinobenzyl 4-{7-[4-(4-amidinobenzylcarbamoyl)piperazin-1-ylcarbonyl]heptanoyl}-1-piperazinecarboxamide (Compound 110); Calculated for $C_{34}H_{48}N_{10}O_4$: MH^+: 661.8, Found: MH^+: 661.3;

1,5-pentamethylene di[4-(4-guanidinophenylacetyl)piperazin-1-ylcarbonyl] (Compound 111); Calculated for $C_{33}H_{46}N_{10}O_4$: MH^+: 647.8, Found: MH^+: 647.3;

1,6-hexamethylene di[4-(4-guanidinophenylacetyl)piperazin-1-ylcarbonyl] (Compound 112); Calculated for $C_{34}H_{48}N_{10}O_4$: MH^+: 661.8, Found: MH^+: 661;

1,7-heptamethylene di[4-(4-guanidinophenylacetyl)piperazin-1-ylcarbonyl] (Compound 113); Calculated for $C_{35}H_{50}N_{10}O_4$: MH^+: 675.9, Found: MH^+: 675.4; and

3-oxa-1,5-pentamethylene di[4-(4-guanidinophenylacetyl)piperazin-1-ylcarbonyl] (Compound 114); Calculated for $C_{32}H_{44}N_{10}O_7$: MH^+: 681.8, Found: MH^+: 681.4.

EXAMPLE 32

In Vitro Assay of Tryptase Inhibition

Mixtures of human tryptase (15 μg/mL) and test compound (varying concentrations) in Tris buffer (comprising: NaCl, 100 mM; Tris, 50 mM; 2-[*N*-morpholine]ethane sulfonic acid, 2.5 mM, $CaCl_2$, 0.5 mM; DMSO, 10%; glycerol, 5%; polyoxyethylenesorbitan monolaurate (Tween-20), 0.05%; heparin, 25 ng/mL; and pH 8.2) were incubated for 1 hour at room temperature and then Tosyl-Gly-Pro-Lys-*para*-nitroanilide was added such that the final concentration of the assay mixture was 0.5 mM. Hydrolysis of the substrate was followed spectrophotometrically at (405 nm) for 5 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

Human tryptase can be purified from human lung and skin tissue samples (e.g., see Smith *et al.* (1984) *J. Biol. Chem.* 59: 11046-11051; and Braganza *et al.* (1991) *Biochem.*

30: 4997-5007) and human mast cell line or obtained commerically (e.g., ICN Biomedicals, Irvine California; Athens Research & Technology, Athens, Georgia). Porcine intestinal mucosa heparin and Tosyl-Gly-Pro-Lys-*para*-nitroanilide can be obtained from Sigma Chemical Company.

Proceeding as described in this application or by methods known to those of ordinary skill the following compounds of Formula I were prepared and tested for tryptase inhibitory activity:

Compound 1, K_i=0.003μM; Compound 2, K_i=0.8μM; Compound 3, K_i=0.07μM; Compound 4, K_i=0.001μM; Compound 5, K_i=0.2μM; Compound 6, K_i=1μM; Compound 7, K_i=0.3μM; Compound 8, K_i=4μM; Compound 9, K_i=0.4μM; Compound 10, K_i=1μM; Compound 11, K_i=0.09μM; Compound 12, K_i=0.2μM; Compound 13, K_i=0.02μM; Compound 14, K_i=0.004μM; Compound 15, K_i=0.5μM; Compound 16, K_i=0.9μM; Compound 17, K_i=1μM; Compound 18, K_i=0.08μM; Compound 19, K_i=1.2μM; Compound 20, K_i=3.4μM; Compound 21, K_i=0.5μM; Compound 22, K_i=0.2μM; Compound 23, K_i=4μM; Compound 24, K_i=0.3μM; Compound 25, K_i=0.002μM; Compound 26, K_i=19μM; Compound 27, K_i=2μM; Compound 28, K_i=4μM; Compound 29, K_i=1μM; Compound 30, K_i=0.031μM; Compound 31, K_i=1μM; Compound 32, K_i=2μM; Compound 33, K_i=1μM; Compound 34, K_i=3μM; Compound 35, K_i=0.8μM; Compound 36, K_i=0.6μM; Compound 37, K_i=0.07μM; Compound 38, K_i=0.004μM; Compound 39, K_i=0.004μM; Compound 40, K_i=4μM; Compound 41, K_i=0.7μM; Compound 42, K_i=0.02μM; Compound 43, K_i=0.4μM; Compound 44, K_i=0.02μM; Compound 45, K_i=0.08μM; Compound 46, K_i=1μM; Compound 47, K_i=0.3μM; Compound 48, K_i=0.09μM; Compound 49, K_i=2μM; Compound 50, K_i=0.08μM; Compound 51, K_i=1μM; Compound 52, K_i=0.04μM; Compound 53, K_i=6μM; Compound 54, K_i=0.1μM; Compound 55, K_i=2μM; Compound 56, K_i=10μM; Compound 57, K_i=2μM; Compound 58, K_i=0.1μM; Compound 59, K_i=0.5μM; Compound 60, K_i=5μM; Compound 61, K_i=41μM; Compound 62, K_i=0.2μM; Compound 63, K_i=2μM;

Compound 64, K_i=1μM; Compound 65, K_i=0.001μM; Compound 66, K_i=0.02μM; Compound 67, K_i=3μM; Compound 68, K_i=0.04μM; Compound 69, K_i=0.5μM; Compound 70, K_i=0.05μM; Compound 71, K_i=0.8μM; Compound 72, K_i=0.1μM; Compound 73, K_i=0.002μM; Compound 74, K_i=0.04μM; Compound 75, K_i=0.01μM; Compound 76, K_i=0.1μM; Compound 77, K_i=6μM; Compound 78, K_i=0.1μM; Compound 79, K_i=1μM; Compound 84, K_i=0.06μM; Compound 85, K_i=0.9μM; Compound 86, K_i=0.08μM; Compound 87, K_i=0.05μM; Compound 88, K_i=0.1μM; Compound 89, K_i=0.1μM; Compound 90, K_i=1μM; Compound 91, K_i=0.1μM; Compound 92, K_i=0.1μM; Compound 93, K_i=0.02μM; Compound 94, K_i=0.007μM; Compound 95, K_i=0.02μM; Compound 96, K_i=0.02μM; Compound 97, K_i=0.0009μM; Compound 98, K_i=0.03μM; Compound 99, K_i=0.05μM; Compound 100, K_i=0.009μM; Compound 101, K_i=0.04μM; Compound 102, K_i=0.08μM; Compound 103, K_i=0.001μM; Compound 104, K_i=0.003μM; Compound 105, K_i=0.04μM; Compound 106, K_i=0.004μM; Compound 107, K_i=0.0001μM; Compound 108, K_i=0.0005μM; Compound 109 K_i=0.0007μM; Compound 110, K_i=0.0008μM; Compound 111, K_i=0.3μM; Compound 112, K_i=0.09μM; Compound 113 K_i=0.005μM; and Compound 114, K_i=0.058μM.

EXAMPLE 33

In Vivo Assay of Asthma

Allergic sheep characterized as dual responders (i.e., displaying early and late phases of bronchoconstriction) are challenged with antigen (e.g., *Ascaris suum*). The sheep are administered test compound or vehicle by aerosol inhalation at 0.5 hours before and at 4 and 24 hours post antigen challenge. Specific lung resistance (SR_L) is monitored via an esophageal balloon catheter just prior to the first test compound or vehicle treatment and every 0.5 to 1 hour thereafter.

In addition, airway responsiveness is monitored 1 to 2 days prior to antigen challenge and just subsequent to administration of test compound or vehicle at 24 hours post antigen challenge. For the purposes of this application, airway responsiveness is defined as the cumulative dose of carbachol required to increase SR_L by 400% (PC_{400}). The PC_{400} values are obtained by

administering 0 to 30 breath units of 1% carbachol (10 mg in 1 mL of PBS) by aerosol inhalation until SR_L was increased by 400%.

Sheep treated with vehicle exhibit early phase bronchoconstriction from 0 to 4 hours post antigen challenge and late phase bronchoconstriction from 4 to greater than 8 hours post antigen challenge. In addition, vehicle treated sheep exhibit hyper responsiveness to carbachol (i.e., a 60% decrease in PC_{400} is observed).

Sheep treated with tryptase inhibitors do not exhibit late phase broncoconstriction (i.e., at 4 to 8 hours post antigen challenge, SR_L remained at basal levels). Further, sheep treated with tryptase inhibitors do not exhibit any hyper responsiveness to carbachol.

EXAMPLE 34

Representative Pharmaceutical Formulations Containing a Compound of Formula I.

ORAL FORMULATION	
Compound of Formula I	10-100 mg
Citric Acid Monohydrate	105 mg
Sodium Hydroxide	18 mg
Flavoring	
Water	q.s. to 100 mL

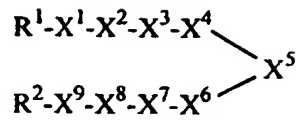
INTRAVENOUS FORMULATION	
Compound of Formula I	0.1-10 mg
Dextrose Monohydrate	q.s. to make isotonic
Citric Acid Monohydrate	1.05 mg
Sodium Hydroxide	0.18 mg
Water for Injection	q.s. to 1.0 mL

TABLET FORMULATION

Compound of Formula I	1%
Microcrystalline Cellulose	73%
Stearic Acid	25%
Colloidal Silica	1%.

WE CLAIM:

1. A compound of Formula I:



I

in which:

X^5 is (C_{3-14})cycloalkylene, hetero(C_{3-14})cycloalkylene, (C_{6-14})arylene or hetero(C_{5-14})arylene;

X^4 and X^6 are independently (C_{0-2})alkylene;

X^1 and X^9 are independently a covalent bond, -C(O)-, -C(O)O-, -OC(O)-, -C(O)N(R^3)-, -N(R^3)C(O)-, -S(O)$_2$N(R^3)-, -N(R^3)S(O)$_2$-, -OC(O)N(R^3)-, -N(R^3)C(O)O-, -N(R^3)C(O)N(R^3)- or -OC(O)O-, wherein each R^3 is independently hydrogen, (C_{1-3})alkyl or (C_{3-8})cycloalkyl, with the proviso that X^1 and X^9 are not both covalent bonds;

X^3 and X^7 are independently -C(O)-, -C(O)O-, -OC(O)-, -C(O)N(R^3)-, -N(R^3)C(O)-, -S(O)$_2$N(R^3)-, -N(R^3)S(O)$_2$-, -OC(O)N(R^3)-, -N(R^3)C(O)O-, -N(R^3)C(O)N(R^3)- or -OC(O)O-, wherein R^3 is as defined above;

X^2 and X^8 are independently (C_{1-8})alkylene, hetero(C_{1-8})alkylene, -X^{10}-X^{11}- or -X^{11}-X^{10}-, wherein X^{10} is (C_{0-4})alkylene or hetero(C_{3-4})alkylene and X^{11} is (C_{3-8})cycloalkylene or hetero(C_{3-8})cycloalkylene;

R^1 is R^4-X^{12}- or R^5-X^{13}-, wherein:

R^4 is amino, amidino, guanidino, 1-iminoethyl or methylamino,

X^{12} is (C_{4-6})alkylene, hetero(C_{4-6})alkylene, heterooxo(C_{4-6})alkylene, oxo(C_{4-6})alkylene or -X^{14}-X^{15}-X^{16}-, wherein X^{15} is (C_{3-6})cycloalkylene, hetero(C_{5-6})arylene, hetero(C_{3-6})cycloalkylene or phenylene, X^{14} is (C_{n14})alkylene and X^{16} is (C_{n16})alkylene, wherein the sum of n14 and n16 is 0, 1, 2, 3 or 4,

R^5 is a group selected from azetidin-3-yl, benzoimidazol-4-yl, benzoimidazol-5-yl

imidazol-1-yl, imidazol-2-yl, imidazol-4-yl, 2-imidazolin-2-yl, 2-imidazolin-3-yl, 2-methylimidazol-1-yl, 4-methylimidazol-1-yl, 5-methylimidazol-1-yl, 1-methylpiperid-3-yl, 1-methylpiperid-4-yl, piperid-3-yl, piperid-4-yl, piperazin-1-yl, piperazin-2-yl, pyrid-3-yl, pyrid-4-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrrolidin-3-yl, 1,4,5,6-tetrahydropyrimidin-2-yl, 1,4,5,6-tetrahydropyrimidin-4-yl and 1,4,5,6-tetrahydropyrimidin-5-yl and any carbocyclic ketone or thioketone derivative thereof, which group is optionally substituted with one or more radicals selected from halo, hydroxy, mercapto, (C_{1-8})alkyl, (C_{3-14})cycloalkyl, (C_{6-14})aryl, (C_{6-14})aryl(C_{1-4})alkyl, (C_{1-8})alkanoyl, (C_{1-8})alkyloxy, (C_{6-14})aryloxy, (C_{3-14})cycloalkyloxy, (C_{1-4})alkyloxy, (C_{1-8})alkylthio, (C_{3-14})cycloalkylthio, (C_{6-14})arylthio and $-NR^6R^7$, wherein R^6 and R^7 are independently selected from hydrogen, (C_{1-8})alkyl, (C_{1-8})alkanoyl, (C_{3-14})cycloalkyl or (C_{6-14})aryl, and X^{13} is (C_{0-6})alkylene, hetero(C_{2-6})alkylene, heterooxo(C_{3-6})alkylene, oxo(C_{2-6})alkylene or $-X^{17}-X^{18}-X^{19}-$, wherein X^{18} is as defined above for X^{15}, X^{17} is (C_{n17})alkylene and

X^{18} is (C_{n18})alkylene, wherein the sum of n17 and n18 is 0, 1 or 2; and

R^2 is $R^8-X^{20}-$ or $R^9-X^{21}-$, wherein:

R^8 is amino, 1-iminoethyl or methylamino,

X^{20} is (C_{4-6})alkylene, hetero(C_{4-6})alkylene, heterooxo(C_{4-6})alkylene, oxo(C_{4-6})alkylene or $-X^{22}-X^{23}-X^{24}-$, wherein X^{23} is as defined above for X^{15}, X^{22} is (C_{n22})alkylene and X^{24} is (C_{n24})alkylene, wherein the sum of n22 and n24 is 0, 1, 2, 3 or 4, with the proviso that when R^8 is amino then X^{22} is not (C_{4-6})alkylene or oxa(C_{4-6})alkylene and n22 is not 1, 2, 3 or 4,

R^9 is as defined above for R^5 and

X^{21} is (C_{0-6})alkylene, hetero(C_{2-6})alkylene, heterooxo(C_{3-6})alkylene, oxo(C_{2-6})alkylene or $-X^{25}-X^{26}-X^{27}-$, wherein X^{26} is as defined above for X^{15}, X^{25} is (C_{n25})alkylene and X^{27} is (C_{n27})alkylene, wherein the sum of n25 and n27 is 0, 1 or 2; wherein each alkylene, cycloalkylene, heterocycloalkylene, phenylene, arylene and heteroarylene, as defined above, are optionally substituted with one or more radicals selected from halo, hydroxy, mercapto, (C_{1-8})alkyl, (C_{3-14})cycloalkyl, (C_{6-14})aryl, (C_{6-14})aryl(C_{1-4})alkyl, (C_{1-8})alkanoyl, (C_{1-8})alkyloxy, (C_{6-14})aryloxy, (C_{3-14})cycloalkyloxy,

(C_{1-4})alkyloxy, (C_{1-8})alkylthio, (C_{3-14})cycloalkylthio, (C_{6-14})arylthio and $-NR^6R^7$, wherein R^6 and R^7 are as defined above; with the proviso that covalent bonds do not occur between heteroatoms contained within R^1, X^2, X^4, X^6, X^8 and R^2 and any heteroatoms contained with X^3, X^5, X^7 and X^9; and

the pharmaceutically acceptable salts, *N*-oxides, prodrug derivatives and protected derivatives thereof.

2. The compound of Claim 1 in which:

X^5 is *cis*-1,5-cyclooctylene and X^4 and X^6 each are a covalent bond or X^5 is 1,4-phenylene and X^4 and X^6 are (C_{0-1})ethylene;

X^1 and X^9 are independently a covalent bond, -C(O)-, -NHC(O)-, -C(O)NH-, $-N(CH_3)C(O)-$ or $-S(O)_2NH-$;

X^3 and X^7 are independently -C(O)- or -C(O)O-;

X^2 and X^8 are independently $-X^{10}-X^{11}-$, wherein:

X^{10} is a covalent bond or methylene and

X^{11} is 4,1-piperidylene or 1,4-piperazinylene;

R^1 is $R^4-X^{12}-$ or $R^5-X^{13}-$, wherein:

R^4 is amidino, guanidino or methylamino,

X^{12} is $-X^{14}-X^{15}-X^{16}-$, wherein X^{15} is 1,4-phenylene or 1,4-piperidylene, X^{14} is (C_{n14})alkylene and X^{16} is (C_{n16})alkylene, wherein the sum of n14 and n16 is 0, 1 or 2,

R^5 is piperid-4-yl and

X^{13} is (C_{2-3})alkylene; and

R^2 is $R^8-X^{20}-$ or $R^9-X^{21}-$, wherein:

R^8 is amino, methylamino or 1-iminoethyl,

X^{20} is $-X^{22}-X^{23}-X^{24}-$, wherein X^{23} is *trans*-1,4-cyclohexylene, 1,4-phenylene, 4,1-pyridylene, 1,4-piperidylene, X^{22} is (C_{n22})alkylene and X^{24} is (C_{n24})alkylene, wherein the sum of n22 and n24 is 1 or 2,

R^9 is benzoimidazol-5-yl, imidazol-1-yl, imidazol-4-yl, 2-imidazolin-2-yl, 4-methylimidazol-1-yl, 5-methylimidazol-1-yl, 1-methylpiperid-4-yl, piperid-4-yl,

piperazin-1-yl, pyrid-3-yl, pyrid-4-yl, 1,4,5,6-tetrahydropyrimidin-5-yl or 1,4,5,6-tetrahydro-2-dioxopyrimidin-5-yl and

X^{21} is (C_{1-6})alkylene, ω-aza(C_{2-5})alkylene, 2-aza-3-oxotrimethylene, 3-aza-2-oxotrimethylene, 3-oxotrimethylene, ω-thia(C_{2-4})alkylene or $-X^{25}-X^{26}-X^{27}-$, wherein X^{26} is 1,4-phenylene, X^{25} is (C_{n25})alkylene and X^{24} is (C_{n27})alkylene, wherein the sum of n25 and n27 is 0 or 1; and

the pharmaceutically acceptable salts, *N*-oxides, prodrug derivatives and protected derivatives thereof.

3. The compound of Claim 2 in which X^5 is *cis*-1,5-cyclooctylene and X^4 and X^6 each are a covalent bond; X^1 and X^9 are independently a covalent bond, -C(O)-, -NHC(O)-, -C(O)NH- or $-S(O)_2NH-$; X^3 and X^7 are independently -C(O)- or -C(O)O-; R^1 is $R^4-X^{12}-$, wherein R^4 is amidino or guanidino; and R^2 is $R^8-X^{20}-$ or $R^9-X^{21}-$, wherein R^8 is amino or methylamino, X^{23} is *trans*-1,4-cyclohexylene or 1,4-phenylene, R^9 is imidazol-1-yl, imidazol-4-yl, 4-methylimidazol-1-yl, 5-methylimidazol-1-yl, piperid-4-yl or pyrid-4-yl and X^{21} is (C_{1-5})alkylene or 3-azatrimethylene; and the pharmaceutically acceptable salts, *N*-oxides, prodrug derivatives and protected derivatives thereof.

4. The compound of Claim 3 in which X^1 and X^9 are independently -C(O)- or -NHC(O)-; X^3 and X^7 each are -C(O)O-; X^2 and X^8 each are $-X^{10}-X^{11}-$, wherein X^{10} is a covalent bond and X^{11} is 1,4-piperazinylene; R^1 is $R^4-X^{12}-$, wherein R^4 is amidino or guanidino and X^{12} is $-X^{14}-X^{15}-X^{16}-$, wherein X^{15} is 1,4-phenylene, X^{14} is a covalent bond and X^{16} is methylene; and R^2 is $R^8-X^{20}-$ or $R^9-X^{21}-$, wherein R^8 is amino, X^{20} is $-X^{22}-X^{23}-X^{24}-$, wherein X^{23} is *trans*-1,4-cyclohexylene, X^{22} is a covalent bond and X^{24} is methylene, R^9 is piperid-4-yl and X^{21} is ethylene or trimethylene; and the pharmaceutically acceptable salts, *N*-oxides, prodrug derivatives and protected derivatives thereof.

5. The compound of Claim 4 in which X^1 and X^9 each are -NHC(O)-, R^1 is 4-amidinobenzyl and R^2 is 2-piperid-4-ylethyl, namely *cis*-1,5-cyclooctylene 4-(4-amidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-(2-piperid-4-ylethylcarbamoyl)-

1-piperazinecarboxylate; and the pharmaceutically acceptable salts, *N*-oxides, prodrug derivatives and protected derivatives thereof.

6. The compound of Claim 4 in which X^1 is -NHC(O)-, X^9 is -C(O)-, R^1 is 4-amidinobenzyl and R^2 is 3-piperid-4-ylpropyl, namely *cis*-1,5-cyclooctylene 4-(4-amidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-(4-piperid-4-ylbutyryl)-1-piperazinecarboxylate; and the pharmaceutically acceptable salts, *N*-oxides, prodrug derivatives and protected derivatives thereof.

7. The compound of Claim 4 in which X^1 and X^9 each are -NHC(O)-, R^1 is 4-guanidinobenzyl and R^2 is *trans*-4-aminocyclohexylmethyl, namely *cis*-1,5-cyclooctylene *trans*-4-(4-aminocyclohexylmethylcarbamoyl)-1-piperazinecarboxylatc 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate; and the pharmaceutically acceptable salts, *N*-oxides, prodrug derivatives and protected derivatives thereof.

8. The compound of Claim 4 in which X^1 and X^9 each are -C(O)-, R^1 is 4-amidinobenzyl and R^2 is 3-piperid-4-ylpropyl, namely *cis*-1,5-cyclooctylene 4-(4-amidinophenylacetyl)-1-piperazinecarboxylate 4-(4-piperid-4-ylbutyryl)-1-piperazinecarboxylate; and the pharmaceutically acceptable salts, *N*-oxides, prodrug derivatives and protected derivatives thereof.

9. The compound of Claim 4 in which X^1 and X^9 each are -NHC(O)-, R^1 is 4-guanidinobenzyl and R^2 is 2-piperid-4-ylethyl, namely *cis*-1,5-cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-(2-piperid-4-ylethylcarbamoyl)-1-piperazinecarboxylate; and the pharmaceutically acceptable salts, *N*-oxides, prodrug derivatives and protected derivatives thereof.

10. The compound of Claim 4 in which X^1 is -NHC(O)-, X^9 is -C(O)-, R^1 is 4-guanidinobenzyl and R^2 is 3-piperid-4-ylpropyl, namely *cis*-1,5-cyclooctylene 4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate 4-(4-piperid-4-ylbutyryl)-

1-piperazinecarboxylate; and the pharmaceutically acceptable salts, *N*-oxides, prodrug derivatives and protected derivatives thereof.

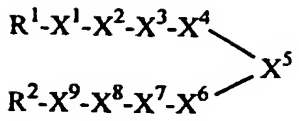
11. The compound of Claim 4 in which X^1 is -C(O)-, X^9 is -NHC(O)-, R^1 is 4-guanidinobenzyl and R^2 is 2-piperid-4-ylethyl, namely *cis*-1,5-cyclooctylene 4-(4-guanidinophenylacetyl)-1-piperazinecarboxylate 4-(2-piperid-4-ylethylcarbamoyl)-1-piperazinecarboxylate; and the pharmaceutically acceptable salts, *N*-oxides, prodrug derivatives and protected derivatives thereof.

12. The compound of Claim 4 in which X^1 and X^9 each are -C(O)-, R^1 is 4-guanidinobenzyl and R^2 is 3-piperid-4-ylpropyl, namely *cis*-1,5-cyclooctylene 4-(4-guanidinophenylacetyl)-1-piperazinecarboxylate 4-(4-piperid-4-ylbutyryl)-1-piperazinecarboxylate; and the pharmaceutically acceptable salts, *N*-oxides, prodrug derivatives and protected derivatives thereof.

13. The compound of Claim 4 in which X^1 is -C(O)-, X^9 is -NHC(O)-, R^1 is 4-amidinobenzyl and R^2 is 2-piperid-4-ylethyl, namely *cis*-1,5-cyclooctylene 4-(4-amidinophenylacetyl)-1-piperazinecarboxylate 4-(2-piperid-4-ylethylcarbamoyl)-1-piperazinecarboxylate; and the pharmaceutically acceptable salts, *N*-oxides, prodrug derivatives and protected derivatives thereof.

14. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1 in combination with a pharmaceutically acceptable excipient.

15. A method of treating a disease in an animal in which tryptase activity contributes to the pathology and/or symptomatology of the disease, which method comprises administering to the animal a therapeutically effective amount of compound of Formula I:



I

in which:

X^5 is (C_{3-14})cycloalkylene, hetero(C_{3-14})cycloalkylene, (C_{6-14})arylene or hetero(C_{5-14})arylene;

X^4 and X^6 are independently (C_{0-2})alkylene;

X^1 and X^3 independently are a covalent bond, -C(O)-, -C(O)O-, -OC(O)-, -C(O)N(R^3)-, -N(R^3)C(O)-, -S(O)$_2$N(R^3)-, -N(R^3)S(O)$_2$-, -OC(O)N(R^3)-, -N(R^3)C(O)O-, -N(R^3)C(O)N(R^3)- or -OC(O)O-, wherein each R^3 is independently hydrogen, (C_{1-3})alkyl or (C_{3-8})cycloalkyl;

X^7 and X^9 are independently -C(O)-, -C(O)O-, -OC(O)-, -C(O)N(R^3)-, -N(R^3)C(O)-, -S(O)$_2$N(R^3)-, -N(R^3)S(O)$_2$-, -OC(O)N(R^3)-, -N(R^3)C(O)O-, -N(R^3)C(O)N(R^3)- or -OC(O)O-, wherein R^3 is as defined above;

X^2 and X^8 are independently (C_{1-8})alkylene, hetero(C_{1-8})alkylene, -X^{10}-X^{11}- or -X^{11}-X^{10}-, wherein X^{10} is (C_{0-4})alkylene or hetero(C_{3-4})alkylene and X^{11} is (C_{3-8})cycloalkylene or hetero(C_{3-8})cycloalkylene;

R^1 is R^4-X^{12}- or R^5-X^{13}-, wherein:

R^4 is amino, amidino, guanidino, 1-iminoethyl or methylamino,

X^{12} is (C_{4-6})alkylene, hetero(C_{4-6})alkylene, heterooxo(C_{4-6})alkylene, oxo(C_{4-6})alkylene or -X^{14}-X^{15}-X^{16}-, wherein X^{15} is (C_{3-6})cycloalkylene, hetero(C_{5-6})arylene, hetero(C_{3-6})cycloalkylene or phenylene, X^{14} is (C_{n14})alkylene and X^{16} is (C_{n16})alkylene, wherein the sum of n14 and n16 is 0, 1, 2, 3 or 4,

R^5 is a group selected from azetidin-3-yl, benzoimidazol-4-yl, benzoimidazol-5-yl imidazol-1-yl, imidazol-2-yl, imidazol-4-yl, 2-imidazolin-2-yl, 2-imidazolin-3-yl, 2-methylimidazol-1-yl, 4-methylimidazol-1-yl, 5-methylimidazol-1-yl, piperid-3-yl, piperid-4-yl, piperazin-1-yl, piperazin-2-yl, pyrid-3-yl, pyrid-4-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrrolidin-3-yl, 1,4,5,6-tetrahydropyrimidin-2-yl, 1,4,5,6-tetrahydropyrimidin-4-yl and 1,4,5,6-tetrahydropyrimidin-5-yl and any

carbocyclic ketone or thioketone derivative thereof, which group is optionally substituted with one or more radicals selected from halo, hydroxy, mercapto, (C_{1-8})alkyl, (C_{3-14})cycloalkyl, (C_{6-14})aryl, (C_{6-14})aryl(C_{1-4})alkyl, (C_{1-8})alkanoyl, (C_{1-8})alkyloxy, (C_{6-14})aryloxy, (C_{3-14})cycloalkyloxy, (C_{1-4})alkyloxy, (C_{1-8})alkylthio, (C_{3-14})cycloalkylthio, (C_{6-14})arylthio and $-NR^6R^7$, wherein R^6 and R^7 are independently selected from hydrogen, (C_{1-8})alkyl, (C_{1-8})alkanoyl, (C_{3-14})cycloalkyl or (C_{6-14})aryl and

X^{13} is (C_{0-6})alkylene, hetero(C_{2-6})alkylene, heterooxo(C_{3-6})alkylene, oxo(C_{2-6})alkylene or $-X^{17}-X^{18}-X^{19}-$, wherein X^{18} is as defined above for X^{15}, X^{17} is (C_{n17})alkylene and X^{18} is (C_{n18})alkylene, wherein the sum of n17 and n18 is 0, 1 or 2; and R^2 is $R^8-X^{20}-$ or $R^9-X^{21}-$, wherein:

R^8 is amino, 1-iminoethyl or methylamino,

X^{20} is (C_{4-6})alkylene, hetero(C_{4-6})alkylene, heterooxo(C_{4-6})alkylene, oxo(C_{4-6})alkylene or $-X^{22}-X^{23}-X^{24}-$, wherein X^{23} is as defined above for X^{15}, X^{22} is (C_{n22})alkylene and X^{24} is (C_{n24})alkylene, wherein the sum of n22 and n24 is 0, 1, 2, 3 or 4, with the proviso that when R^8 is amino then X^{22} is not (C_{4-6})alkylene or oxa(C_{4-6})alkylene and n22 is not 1, 2, 3 or 4,

R^9 is as defined above for R^5 and

X^{21} is (C_{0-6})alkylene, hetero(C_{2-6})alkylene, heterooxo(C_{3-6})alkylene, oxo(C_{2-6})alkylene or $-X^{25}-X^{26}-X^{27}-$, wherein X^{26} is as defined above for X^{15}, X^{25} is (C_{n25})alkylene and X^{27} is (C_{n27})alkylene, wherein the sum of n25 and n27 is 0, 1 or 2; wherein each alkylene, cycloalkylene, heterocycloalkylene, phenylene, arylene and heteroarylene, as defined above, are optionally substituted with one or more radicals selected from halo, hydroxy, mercapto, (C_{1-8})alkyl, (C_{3-14})cycloalkyl, (C_{6-14})aryl, (C_{6-14})aryl(C_{1-4})alkyl, (C_{1-8})alkanoyl, (C_{1-8})alkyloxy, (C_{6-14})aryloxy, (C_{3-14})cycloalkyloxy, (C_{1-4})alkyloxy, (C_{1-8})alkylthio, (C_{3-14})cycloalkylthio, (C_{6-14})arylthio and $-NR^6R^7$, wherein R^6 and R^7 are as defined above; with the proviso that covalent bonds do not occur between heteroatoms contained within R^1, X^2, X^4, X^6, X^8 and R^2 and any heteroatoms contained with X^3, X^5, X^7 and X^9; or

a pharmaceutically acceptable salt, *N*-oxide or prodrug derivative thereof.

16. The method of Claim 15 in which the disease is selected from asthma, allergic rhinitis, rheumatoid spodylitis, osteoarthritis, gouty arthritis, rheumatoid arthritis, arthritic conditions in general, urticaria, angioedema, eczematous dermatitis, anaphylaxis, hyper proliferative skin disease, peptic ulcers, inflammatory bowel disease, ocular and vernal conjunctivitis and inflammatory skin conditions.

17. The method of Claim 16 in which the disease is asthma.

18. The method of Claim 17 in which the pharmaceutical composition comprises a therapeutically effective amount of a compound of Formula I in a aerosolized pharmaceutically acceptable carrier suitable for administration as an inhalant.

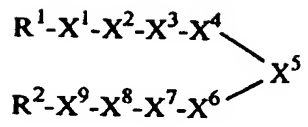
19. The method of Claim 18 in which the pharmaceutical composition further comprises a therapeutically effective amount of a β-adrenergic agonist, a methylxanthine, a cromoglycate or a corticosteroid.

20. The method of Claim 19 in which the β-adrenergic agonist is selected from albuterol, terbutaline, formoterol, fenoterol and prenaline, the methylxanthine is selected from caffeine, theophylline, aminophylline and theobromine, the cromoglycate is selected from cromolyn and nedocromil and the corticosteriod is selected from beclomethasome, triamcinolone, flurisolide and dexamethasone.

21. The method of Claim 16 in which the disease is rheumatoid arthritis or conjunctivitis.

22. The method of Claim 21 in which the pharmaceutical composition comprises a therapeutically effective amount of a compound of Formula I in a pharmaceutically acceptable carrier suitable for topical administration.

23. A compound of Formula I:



I

in which:

X^4-X^5-X^6 together are (C_{2-12})alkylene or hetero(C_{3-12})alkylene;

X^1 and X^9 are independently a covalent bond, -C(O)-, -C(O)O-, -OC(O)-, -C(O)N(R^3)-, -N(R^3)C(O)-, -$S(O)_2$N(R^3)-, -N(R^3)$S(O)_2$-, -OC(O)N(R^3)-, -N(R^3)C(O)O-, -N(R^3)C(O)N(R^3)- or -OC(O)O-, wherein each R^3 is independently hydrogen, (C_{1-3})alkyl or (C_{3-8})cycloalkyl, with the proviso that X^1 and X^9 are not both covalent bonds;

X^3 and X^7 are independently -C(O)-, -C(O)O-, -OC(O)-, -C(O)N(R^3)-, -N(R^3)C(O)-, -$S(O)_2$N(R^3)-, -N(R^3)$S(O)_2$-, -OC(O)N(R^3)-, -N(R^3)C(O)O-, -N(R^3)C(O)N(R^3)- or -OC(O)O-, wherein R^3 is as defined above;

X^2 and X^8 are independently (C_{1-8})alkylene, hetero(C_{1-8})alkylene, -X^{10}-X^{11}- or -X^{11}-X^{10}-, wherein X^{10} is (C_{0-4})alkylene or hetero(C_{3-4})alkylene and X^{11} is (C_{3-8})cycloalkylene or hetero(C_{3-8})cycloalkylene;

R^1 is R^4-X^{12}- or R^5-X^{13}-, wherein:

R^4 is amino, amidino, guanidino, 1-iminoethyl or methylamino,

X^{12} is (C_{4-6})alkylene, hetero(C_{4-6})alkylene, heterooxo(C_{4-6})alkylene, oxo(C_{4-6})alkylene or -X^{14}-X^{15}-X^{16}-, wherein X^{15} is (C_{3-6})cycloalkylene, hetero(C_{5-6})arylene, hetero(C_{3-6})cycloalkylene or phenylene, X^{14} is (C_{n14})alkylene and X^{16} is (C_{n16})alkylene, wherein the sum of n14 and n16 is 0, 1, 2, 3 or 4,

R^5 is a group selected from azetidin-3-yl, benzoimidazol-4-yl, benzoimidazol-5-yl imidazol-1-yl, imidazol-2-yl, imidazol-4-yl, 2-imidazolin-2-yl, 2-imidazolin-3-yl, 2-methylimidazol-1-yl, 4-methylimidazol-1-yl, 5-methylimidazol-1-yl, 1-methylpiperid-3-yl, 1-methylpiperid-4-yl, piperid-3-yl, piperid-4-yl, piperazin-1-yl, piperazin-2-yl, pyrid-3-yl, pyrid-4-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrrolidin-3-yl, 1,4,5,6-tetrahydropyrimidin-2-yl, 1,4,5,6-tetrahydropyrimidin-4-yl and

1,4,5,6-tetrahydropyrimidin-5-yl and any carbocyclic ketone or thioketone derivative thereof, which group is optionally substituted with one or more radicals selected from halo, hydroxy, mercapto, (C_{1-8})alkyl, (C_{3-14})cycloalkyl, (C_{6-14})aryl, (C_{6-14})aryl(C_{1-4})alkyl, (C_{1-8})alkanoyl, (C_{1-8})alkyloxy, (C_{6-14})aryloxy, (C_{3-14})cycloalkyloxy, (C_{1-4})alkyloxy, (C_{1-8})alkylthio, (C_{3-14})cycloalkylthio, (C_{6-14})arylthio and $-NR^6R^7$, wherein R^6 and R^7 are independently selected from hydrogen, (C_{1-8})alkyl, (C_{1-8})alkanoyl, (C_{3-14})cycloalkyl or (C_{6-14})aryl and

X^{13} is (C_{0-6})alkylene, hetero(C_{2-6})alkylene, heterooxo(C_{3-6})alkylene, oxo(C_{2-6})alkylene or $-X^{17}-X^{18}-X^{19}-$, wherein X^{18} is as defined above for X^{15}, X^{17} is (C_{n17})alkylene and X^{18} is (C_{n18})alkylene, wherein the sum of n17 and n18 is 0, 1 or 2; and R^2 is $R^8-X^{20}-$ or $R^9-X^{21}-$, wherein:

R^8 is as defined above for R^4,

X^{20} is (C_{4-6})alkylene, hetero(C_{4-6})alkylene, heterooxo(C_{4-6})alkylene, oxo(C_{4-6})alkylene or $-X^{22}-X^{23}-X^{24}-$, wherein X^{23} is as defined above for X^{15}, X^{22} is (C_{n22})alkylene and X^{24} is (C_{n24})alkylene, wherein the sum of n22 and n24 is 0, 1, 2, 3 or 4,

R^9 is as defined above for R^5 and

X^{21} is (C_{0-6})alkylene, hetero(C_{2-6})alkylene, heterooxo(C_{3-6})alkylene, oxo(C_{2-6})alkylene or $-X^{25}-X^{26}-X^{27}-$, wherein X^{26} is as defined above for X^{15}, X^{25} is (C_{n25})alkylene and X^{27} is (C_{n27})alkylene, wherein the sum of n25 and n27 is 0, 1 or 2;

wherein each alkylene, cycloalkylene, heteroalkylene, heterocycloalkylene, phenylene, arylene and heteroarylene, as defined above, are optionally substituted with one or more radicals selected from halo, hydroxy, mercapto, (C_{1-8})alkyl, (C_{3-14})cycloalkyl, (C_{6-14})aryl, (C_{6-14})aryl(C_{1-4})alkyl, (C_{1-8})alkanoyl, (C_{1-8})alkyloxy, (C_{6-14})aryloxy, (C_{3-14})cycloalkyloxy, (C_{1-4})alkyloxy, (C_{1-8})alkylthio, (C_{3-14})cycloalkylthio, (C_{6-14})arylthio and $-NR^6R^7$, wherein R^6 and R^7 are as defined above; with the proviso that covalent bonds do not occur between heteroatoms contained within R^1, X^2, X^4, X^6, X^8 and R^2 and any heteroatoms contained with X^3, X^5, X^7 and X^9; and

the pharmaceutically acceptable salts, *N*-oxides, prodrug derivatives and protected derivatives thereof.

24. The compound of Claim 23 in which:

X^4-X^5-X^6 together are (C_{2-10})alkylene or hetero(C_{3-10})alkylene;

X^1 and X^9 are independently a covalent bond, -C(O)-, -NHC(O)-, -C(O)NH-, $-N(CH_3)C(O)-$ or $-S(O)_2NH-$;

X^3 and X^7 are independently -C(O)- or -C(O)O-;

X^2 and X^8 are independently $-X^{10}-X^{11}-$, wherein X^{10} is a covalent bond or methylene and X^{11} is 4,1-piperidylene or 1,4-piperazinylene;

R^1 is R^4-X^{12}- or R^5-X^{13}-, wherein:

R^4 is amidino, guanidino or methylamino,

X^{12} is $-X^{14}-X^{15}-X^{16}-$, wherein X^{15} is 1,4-phenylene or 1,4-piperidylene, X^{14} is (C_{n14})alkylene and X^{16} is (C_{n16})alkylene, wherein the sum of n14 and n16 is 0, 1 or 2,

R^5 is piperid-4-yl and

X^{13} is (C_{2-3})alkylene; and

R^2 is R^8-X^{20}- or R^9-X^{21}-, wherein:

R^8 is amino, amidino, guanidino, methylamino or 1-iminoethyl,

X^{20} is $-X^{22}-X^{23}-X^{24}-$, wherein X^{23} is *trans*-1,4-cyclohexylene, 1,4-phenylene, 4,1-pyridylene, 1,4-piperidylene, X^{22} is (C_{n22})alkylene and X^{24} is (C_{n24})alkylene, wherein the sum of n22 and n24 is 1 or 2,

R^9 is benzoimidazol-5-yl, imidazol-1-yl, imidazol-4-yl, 2-imidazolin-2-yl, 4-methylimidazol-1-yl, 5-methylimidazol-1-yl, 1-methylpiperid-4-yl, piperid-4-yl, piperazin-1-yl, pyrid-3-yl, pyrid-4-yl, 1,4,5,6-tetrahydropyrimidin-5-yl or 1,4,5,6-tetrahydro-2-dioxopyrimidin-5-yl and

X^{21} is (C_{1-6})alkylene, ω-aza(C_{2-5})alkylene, 2-aza-3-oxotrimethylene, 3-aza-2-oxotrimethylene, 3-oxotrimethylene, ω-thia(C_{2-4})alkylene or $-X^{25}-X^{26}-X^{27}-$, wherein X^{26} is 1,4-phenylene, X^{25} is (C_{n25})alkylene and X^{24} is (C_{n27})alkylene, wherein the sum of n25 and n27 is 0 or 1; and

the pharmaceutically acceptable salts, *N*-oxides, prodrug derivatives and protected derivatives thereof.

25. The compound of Claim 24 in which X^4-X^5-X^6 together are (C_{4-8})alkylene or

hetero(C_{4-10})alkylene; X^1 and X^9 are independently a covalent bond, -C(O)-, -NHC(O)-, -C(O)NH- or -$S(O)_2$NH-; X^3 and X^7 are independently -C(O)- or -C(O)O-; R^1 is R^4-X^{12}-, wherein R^4 is amidino or guanidino; and R^2 is R^8-X^{20}- or R^9-X^{21}-, wherein R^8 is amino, amidino, guanidino or methylamino, X^{23} is *trans*-1,4-cyclohexylene or 1,4-phenylene, R^9 is imidazol-1-yl, imidazol-4-yl, 4-methylimidazol-1-yl, 5-methylimidazol-1-yl, piperid-4-yl or pyrid-4-yl and X^{21} is (C_{1-5})alkylene or 3-azatrimethylene; and the pharmaceutically acceptable salts, *N*-oxides, prodrug derivatives and protected derivatives thereof.

26. The compound of Claim 25 in which X^1 and X^9 are independently -C(O)- or -NHC(O)-; X^3 and X^7 are independently -C(O)- or -C(O)O-; X^2 and X^8 each are -X^{10}-X^{11}-, wherein X^{10} is a covalent bond and X^{11} is 1,4-piperazinylene; R^1 is R^4-X^{12}-, wherein R^4 is amidino or guanidino and X^{12} is -X^{14}-X^{15}-X^{16}-, wherein X^{15} is 1,4-phenylene, X^{14} is a covalent bond and X^{16} is methylene; and R^2 is R^8-X^{20}-, wherein R^8 is amidino or quanidino and X^{20} is -X^{22}-X^{23}-X^{24}-, wherein X^{23} is 1,4-phenylene, X^{22} is a covalent bond and X^{24} is methylene; and the pharmaceutically acceptable salts, *N*-oxides, prodrug derivatives and protected derivatives thereof.

27. The compound of Claim 26 in which X^4-X^5-X^6 together are hexamethylene; X^1 and X^9 each are -NHC(O)-, X^3 and X^7 each are -C(O)- and R^1 and R^2 each are 4-guanidinobenzyl, namely 4-guanidinobenzyl 4-{7-[4-(4-guanidinobenzylcarbamoyl)piperazin-1-ylcarbonyl]heptanoyl}-1-piperazinecarboxamide; and the pharmaceutically acceptable salts, *N*-oxides, prodrug derivatives and protected derivatives thereof.

28. The compound of Claim 26 in which X^4-X^5-X^6 together are heptamethylene; X^1 and X^9 each are -NHC(O)-, X^3 and X^7 each are -C(O)- and R^1 and R^2 each are 4-guanidinobenzyl, namely 4-guanidinobenzyl 4-{8-[4-(4-guanidinobenzylcarbamoyl)piperazin-1-ylcarbonyl]octanoyl}-1-piperazinecarboxamide; and the pharmaceutically acceptable salts, *N*-oxides, prodrug derivatives and protected derivatives thereof.

29. The compound of Claim 26 in which X^4-X^5-X^6 together are octamethylene; X^1 and X^9 each are -NHC(O)-, X^3 and X^7 each are -C(O)- and R^1 and R^2 each are 4-guanidinobenzyl, namely 4-guanidinobenzyl 4-{9-[4-(4-guanidinobenzylcarbamoyl)piperazin-1-ylcarbonyl]nonanoyl}-1-piperazinecarboxamide; and the pharmaceutically acceptable salts, *N*-oxides, prodrug derivatives and protected derivatives thereof.

30. The compound of Claim 26 in which X^4-X^5-X^6 together are hexamethylene; X^1 and X^9 each are -NHC(O)-, X^3 and X^7 each are -C(O)- and R^1 and R^2 each are 4-amidinobenzyl, namely 4-amidinobenzyl 4-{7-[4-(4-amidinobenzylcarbamoyl)piperazin-1-ylcarbonyl]heptanoyl}-1-piperazinecarboxamide; and the pharmaceutically acceptable salts, *N*-oxides, prodrug derivatives and protected derivatives thereof.

31. The compound of Claim 26 in which X^4-X^5-X^6 together are pentamethylene; X^1 and X^9 each are -NHC(O)-, X^3 and X^7 each are -C(O)O- and R^1 and R^2 each are 4-guanidinobenzyl, namely 1,5-pentamethylene di[4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate]; and the pharmaceutically acceptable salts, *N*-oxides, prodrug derivatives and protected derivatives thereof.

32. The compound of Claim 26 in which X^4-X^5-X^6 together are tetramethylene; X^1 and X^9 each are -NHC(O)-, X^3 and X^7 each are -C(O)O- and R^1 and R^2 each are 4-guanidinobenzyl, namely 1,5-tetramethylene di[4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate]; and the pharmaceutically acceptable salts, *N*-oxides, prodrug derivatives and protected derivatives thereof.

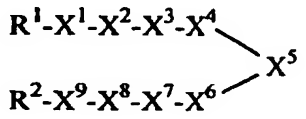
33. The compound of Claim 26 in which X^4-X^5-X^6 together are pentamethylene; X^1 and X^9 each are -NHC(O)-, X^3 and X^7 each are -C(O)- and R^1 and R^2 each are 4-guanidinobenzyl, namely 4-guanidinobenzyl 4-{6-[4-(4-amidinobenzylcarbamoyl)piperazin-1-ylcarbonyl]hexanoyl}-

1-piperazinecarboxamide; and the pharmaceutically acceptable salts, *N*-oxides, prodrug derivatives and protected derivatives thereof.

34. The compound of Claim 26 in which X^4-X^5-X^6 together are 3-oxatetramethylene; X^1 and X^9 each are -C(O)-, X^3 and X^7 each are -C(O)- and R^1 and R^2 each are 4-amidinobenzyl, namely 3-oxa-1,5-pentamethylene di[4-(4-guanidinophenylacetyl)piperazin-1-ylcarbonyl]; and the pharmaceutically acceptable salts, *N*-oxides, prodrug derivatives and protected derivatives thereof.

35. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 23 in combination with a pharmaceutically acceptable excipient.

36. A method of treating a disease in an animal in which tryptase activity contributes to the pathology and/or symptomatology of the disease, which method comprises administering to the animal a therapeutically effective amount of compound of Formula I:



I

in which:

X^4-X^5-X^6 together are (C_{2-12})alkylene or hetero(C_{3-12})alkylene;

X^1 and X^9 are independently a covalent bond, -C(O)-, -C(O)O-, -OC(O)-, -C(O)N(R^3)-, -N(R^3)C(O)-, -S(O)$_2$N(R^3)-, -N(R^3)S(O)$_2$-, -OC(O)N(R^3)-, -N(R^3)C(O)O-, -N(R^3)C(O)N(R^3)- or -OC(O)O-, wherein each R^3 is independently hydrogen, (C_{1-3})alkyl or (C_{3-8})cycloalkyl, with the proviso that X^1 and X^9 are not both covalent bonds;

X^3 and X^7 are independently -C(O)-, -C(O)O-, -OC(O)-, -C(O)N(R^3)-, -N(R^3)C(O)-, -S(O)$_2$N(R^3)-, -N(R^3)S(O)$_2$-, -OC(O)N(R^3)-, -N(R^3)C(O)O-, -N(R^3)C(O)N(R^3)- or -OC(O)O-, wherein R^3 is as defined above;

X^2 and X^8 are independently (C_{1-8})alkylene, hetero(C_{1-8})alkylene, $-X^{10}-X^{11}-$ or $-X^{11}-X^{10}-$, wherein X^{10} is (C_{0-4})alkylene or hetero(C_{3-4})alkylene and X^{11} is (C_{3-8})cycloalkylene or hetero(C_{3-8})cycloalkylene;

R^1 is $R^4-X^{12}-$ or $R^5-X^{13}-$, wherein:

R^4 is amino, amidino, guanidino, 1-iminoethyl or methylamino,

X^{12} is (C_{4-6})alkylene, hetero(C_{4-6})alkylene, heterooxo(C_{4-6})alkylene, oxo(C_{4-6})alkylene or $-X^{14}-X^{15}-X^{16}-$, wherein X^{15} is (C_{3-6})cycloalkylene, hetero(C_{5-6})arylene, hetero(C_{3-6})cycloalkylene or phenylene, X^{14} is (C_{n14})alkylene and X^{16} is (C_{n16})alkylene, wherein the sum of n14 and n16 is 0, 1, 2, 3 or 4,

R^5 is a group selected from azetidin-3-yl, benzoimidazol-4-yl, benzoimidazol-5-yl imidazol-1-yl, imidazol-2-yl, imidazol-4-yl, 2-imidazolin-2-yl, 2-imidazolin-3-yl, 2-methylimidazol-1-yl, 4-methylimidazol-1-yl, 5-methylimidazol-1-yl, 1-methylpiperid-3-yl, 1-methylpiperid-4-yl, piperid-3-yl, piperid-4-yl, piperazin-1-yl, piperazin-2-yl, pyrid-3-yl, pyrid-4-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrrolidin-3-yl, 1,4,5,6-tetrahydropyrimidin-2-yl, 1,4,5,6-tetrahydropyrimidin-4-yl and 1,4,5,6-tetrahydropyrimidin-5-yl and any carbocyclic ketone or thioketone derivative thereof, which group is optionally substituted with one or more radicals selected from halo, hydroxy, mercapto, (C_{1-8})alkyl, (C_{3-14})cycloalkyl, (C_{6-14})aryl, (C_{6-14})aryl(C_{1-4})alkyl, (C_{1-8})alkanoyl, (C_{1-8})alkyloxy, (C_{6-14})aryloxy, (C_{3-14})cycloalkyloxy, (C_{1-4})alkyloxy, (C_{1-8})alkylthio, (C_{3-14})cycloalkylthio, (C_{6-14})arylthio and $-NR^6R^7$, wherein R^6 and R^7 are independently selected from hydrogen, (C_{1-8})alkyl, (C_{1-8})alkanoyl, (C_{3-14})cycloalkyl or (C_{6-14})aryl and

X^{13} is (C_{0-6})alkylene, hetero(C_{2-6})alkylene, heterooxo(C_{3-6})alkylene, oxo(C_{2-6})alkylene or $-X^{17}-X^{18}-X^{19}-$, wherein X^{18} is as defined above for X^{15}, X^{17} is (C_{n17})alkylene and X^{18} is (C_{n18})alkylene, wherein the sum of n17 and n18 is 0, 1 or 2; and

R^2 is $R^8-X^{20}-$ or $R^9-X^{21}-$, wherein:

R^8 is as defined above for R^4,

X^{20} is (C_{4-6})alkylene, hetero(C_{4-6})alkylene, heterooxo(C_{4-6})alkylene, oxo(C_{4-6})alkylene or $-X^{22}-X^{23}-X^{24}-$, wherein X^{23} is as defined above for X^{15}, X^{22} is (C_{n22})alkylene and X^{24} is (C_{n24})alkylene, wherein the sum of n22 and n24 is 0, 1, 2, 3 or 4,

R^9 is as defined above for R^5 and

X^{21} is (C_{0-6})alkylene, hetero(C_{2-6})alkylene, heterooxo(C_{3-6})alkylene, oxo(C_{2-6})alkylene or $-X^{25}-X^{26}-X^{27}-$, wherein X^{26} is as defined above for X^{15}, X^{25} is (C_{n25})alkylene and X^{27} is (C_{n27})alkylene, wherein the sum of n25 and n27 is 0, 1 or 2; wherein each alkylene, cycloalkylene, heteroalkylene, heterocycloalkylene, phenylene, arylene and heteroarylene, as defined above, are optionally substituted with one or more radicals selected from halo, hydroxy, mercapto, (C_{1-8})alkyl, (C_{3-14})cycloalkyl, (C_{6-14})aryl, (C_{6-14})aryl(C_{1-4})alkyl, (C_{1-8})alkanoyl, (C_{1-8})alkyloxy, (C_{6-14})aryloxy, (C_{3-14})cycloalkyloxy, (C_{1-4})alkyloxy, (C_{1-8})alkylthio, (C_{3-14})cycloalkylthio, (C_{6-14})arylthio and $-NR^6R^7$, wherein R^6 and R^7 are as defined above; with the proviso that covalent bonds do not occur between heteroatoms contained within R^1, X^2, X^4, X^6, X^8 and R^2 and any heteroatoms contained with X^3, X^5, X^7 and X^9; or

a pharmaceutically acceptable salt, *N*-oxide or prodrug derivative thereof.

37. The method of Claim 36 in which the disease is selected from asthma, allergic rhinitis, rheumatoid spodylitis, osteoarthritis, gouty arthritis, rheumatoid arthritis, arthritic conditions in general, urticaria, angioedema, eczematous dermatitis, anaphylaxis, hyper proliferative skin disease, peptic ulcers, inflammatory bowel disease, ocular and vernal conjunctivitis and inflammatory skin conditions.

38. The method of Claim 37 in which the disease is asthma.

39. The method of Claim 38 in which the pharmaceutical composition comprises a therapeutically effective amount of a compound of Formula I in a aerosolized pharmaceutically acceptable carrier suitable for administration as an inhalant.

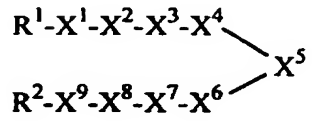
40. The method of Claim 39 in which the pharmaceutical composition further comprises a therapeutically effective amount of a β-adrenergic agonist, a methylxanthine, a cromoglycate or a corticosteroid.

41. The method of Claim 40 in which the β-adrenergic agonist is selected from albuterol, terbutaline, formoterol, fenoterol and prenaline, the methylxanthine is selected from caffeine, theophylline, aminophylline and theobromine, the cromoglycate is selected from cromolyn and nedocromil and the corticosteriod is selected from beclomethasome, triamcinolone, flurisolide and dexamethasone.

42. The method of Claim 37 in which the disease is rheumatoid arthritis or conjunctivitis.

43. The method of Claim 42 in which the pharmaceutical composition comprises a therapeutically effective amount of a compound of Formula I in a pharmaceutically acceptable carrier suitable for topical administration.

44. A process for preparing a compound of Formula I:



I

in which:

X^5 is (C_{3-14})cycloalkylene, hetero(C_{3-14})cycloalkylene, (C_{6-14})arylene or hetero(C_{5-14})arylene and X^4 and X^6 are independently (C_{0-2})alkylene or X^4-X^5-X^6 together are (C_{2-12})alkylene or hetero(C_{3-12})alkylene;

X^1 and X^9 are independently a covalent bond, -C(O)-, -C(O)O-, -OC(O)-, -C(O)N(R^3)-, -N(R^3)C(O)-, -S(O)$_2$N(R^3)-, -N(R^3)S(O)$_2$-, -OC(O)N(R^3)-, -N(R^3)C(O)O-, -N(R^3)C(O)N(R^3)- or -OC(O)O-, wherein each R^3 is independently hydrogen, (C_{1-3})alkyl or (C_{3-8})cycloalkyl, with the proviso that X^1 and X^9 are not both covalent bonds;

X^3 and X^7 are independently -C(O)-, -C(O)O-, -OC(O)-, -C(O)N(R^3)-, -N(R^3)C(O)-, -S(O)$_2$N(R^3)-, -N(R^3)S(O)$_2$-, -OC(O)N(R^3)-, -N(R^3)C(O)O-, -N(R^3)C(O)N(R^3)- or -OC(O)O-, wherein R^3 is as defined above;

X^2 and X^8 are independently (C_{1-8})alkylene, hetero(C_{1-8})alkylene, -X^{10}-X^{11}- or -X^{11}-X^{10}-, wherein X^{10} is (C_{0-4})alkylene or hetero(C_{3-4})alkylene and X^{11} is (C_{3-8})cycloalkylene or hetero(C_{3-8})cycloalkylene;

R^1 is R^4-X^{12}- or R^5-X^{13}-, wherein:

R^4 is amino, amidino, guanidino, 1-iminoethyl or methylamino,

X^{12} is (C_{4-6})alkylene, hetero(C_{4-6})alkylene, heterooxo(C_{4-6})alkylene, oxo(C_{4-6})alkylene or -X^{14}-X^{15}-X^{16}-, wherein X^{15} is (C_{3-6})cycloalkylene, hetero(C_{5-6})arylene, hetero(C_{3-6})cycloalkylene or phenylene,

X^{14} is (C_{n14})alkylene and X^{16} is (C_{n16})alkylene, wherein the sum of n14 and n16 is 0, 1, 2, 3 or 4,

R^5 is a group selected from azetidin-3-yl, benzoimidazol-4-yl, benzoimidazol-5-yl imidazol-1-yl, imidazol-2-yl, imidazol-4-yl, 2-imidazolin-2-yl, 2-imidazolin-3-yl,

2-methylimidazol-1-yl, 4-methylimidazol-1-yl, 5-methylimidazol-1-yl, 1-methylpiperid-3-yl, 1-methylpiperid-4-yl, piperid-3-yl, piperid-4-yl, piperazin-1-yl, piperazin-2-yl, pyrid-3-yl, pyrid-4-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrrolidin-3-yl, 1,4,5,6-tetrahydropyrimidin-2-yl, 1,4,5,6-tetrahydropyrimidin-4-yl and 1,4,5,6-tetrahydropyrimidin-5-yl and any carbocyclic ketone or thioketone derivative thereof, which group is optionally substituted with one or more radicals selected from halo, hydroxy, mercapto, (C_{1-8})alkyl, (C_{3-14})cycloalkyl, (C_{6-14})aryl, (C_{6-14})aryl(C_{1-4})alkyl, (C_{1-8})alkanoyl, (C_{1-8})alkyloxy, (C_{6-14})aryloxy, (C_{3-14})cycloalkyloxy, (C_{1-4})alkyloxy, (C_{1-8})alkylthio, (C_{3-14})cycloalkylthio, (C_{6-14})arylthio and $-NR^6R^7$, wherein R^6 and R^7 are independently selected from hydrogen, (C_{1-8})alkyl, (C_{1-8})alkanoyl, (C_{3-14})cycloalkyl or (C_{6-14})aryl and

X^{13} is (C_{0-6})alkylene, hetero(C_{2-6})alkylene, heterooxo(C_{3-6})alkylene, oxo(C_{2-6})alkylene or $-X^{17}-X^{18}-X^{19}-$, wherein X^{18} is as defined above for X^{15}, X^{17} is (C_{n17})alkylene and X^{18} is (C_{n18})alkylene, wherein the sum of n17 and n18 is 0, 1 or 2; and R^2 is $R^8-X^{20}-$ or $R^9-X^{21}-$, wherein:

R^8 is amino, 1-iminoethyl or methylamino,

X^{20} is (C_{4-6})alkylene, hetero(C_{4-6})alkylene, heterooxo(C_{4-6})alkylene, oxo(C_{4-6})alkylene or $-X^{22}-X^{23}-X^{24}-$, wherein X^{23} is as defined above for X^{15}, X^{22} is (C_{n22})alkylene and X^{24} is (C_{n24})alkylene, wherein the sum of n22 and n24 is 0, 1, 2, 3 or 4, with the proviso that when R^8 is amino then X^{22} is not (C_{4-6})alkylene or oxa(C_{4-6})alkylene and n22 is not 1, 2, 3 or 4,

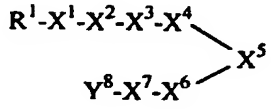
R^9 is as defined above for R^5 and

X^{21} is (C_{0-6})alkylene, hetero(C_{2-6})alkylene, heterooxo(C_{3-6})alkylene, oxo(C_{2-6})alkylene or $-X^{25}-X^{26}-X^{27}-$, wherein X^{26} is as defined above for X^{15}, X^{25} is (C_{n25})alkylene and X^{27} is (C_{n27})alkylene, wherein the sum of n25 and n27 is 0, 1 or 2; wherein each alkylene, cycloalkylene, heterocycloalkylene, phenylene, arylene and heteroarylene, as defined above, are optionally substituted with one or more radicals selected from halo, hydroxy, mercapto, (C_{1-8})alkyl, (C_{3-14})cycloalkyl, (C_{6-14})aryl, (C_{6-14})aryl(C_{1-4})alkyl, (C_{1-8})alkanoyl, (C_{1-8})alkyloxy, (C_{6-14})aryloxy, (C_{3-14})cycloalkyloxy, (C_{1-4})alkyloxy, (C_{1-8})alkylthio, (C_{3-14})cycloalkylthio, (C_{6-14})arylthio and $-NR^6R^7$, wherein

R^6 and R^7 are as defined above; with the proviso that covalent bonds do not occur between heteroatoms contained within R^1, X^2, X^4, X^6, X^8 and R^2 and any heteroatoms contained with X^3, X^5, X^7 and X^9; and

the pharmaceutically acceptable salts, *N*-oxides, prodrug derivatives and protected derivatives thereof, which process comprises:

(a) reacting a compound of Formula 1:

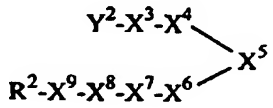


1

or a protected derivative thereof, with a compound of the formula R^2-Y^9-C(O)L, or a protected derivative thereof, wherein L is a leaving group, Y^9 is a bond, -O- or -N(R^3)-, Y^8 is piperazin-1-yl, piperid-4-yl or HN(R^3)-(C_{1-8})alkyl, respectively, and each R^1, R^2, R^3, X^1, X^2, X^3, X^4, X^5, X^6 and X^7 are as defined in the Summary of the Invention, and then deprotecting when necessary, to give a compound of Formula I, in which X^8 is 1,4-piperazinylene or 1,4-piperidylene and X^9 is -C(O)-, -OC(O)- or -N(R^3)C(O)- or in which X^8 is (C_{1-8})alkylene and X^9 is -C(O)N(R^3)-, -OC(O)N(R^3)- or -N(R^3)C(O)N(R^3)-;

(b) reacting a compound of Formula 1, or a protected derivative thereof, with an isocyanate of the formula R^2-NC(O), or a protected derivative thereof, and then deprotecting when necessary, to give a compound of Formula I in which X^8 is 1,4-piperazinylene or 1,4-piperidylene and X^9 is -NHC(O)- or in which X^8 is (C_{1-8})alkylene and X^9 is -NHC(O)N(R^3)-;

(c) reacting a compound of Formula 2:

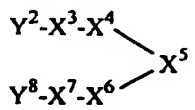


2

or a protected derivative thereof, with a compound of the formula R^1-Y^1-C(O)L, or a protected derivative thereof, wherein L is a leaving group, Y^1 is a bond, -O- or -N(R^3)-, Y^2 is piperazin-1-yl, piperid-4-yl or HN(R^3)-(C_{1-8})alkyl, respectively, and each R^1, R^2, R^3, X^3, X^4, X^5, X^6, X^7, X^8 and X^9 are as defined in the Summary of the Invention, and then deprotecting when necessary, to give a compound of Formula I in which X^2 is 1,4-piperazinylene or 1,4-piperidylene and X^1 is -C(O)-, -OC(O)- or -N(R^3)C(O)- or in which X^2 is (C_{1-8})alkylene and X^1 is -C(O)N(R^3)-, -OC(O)N(R^3)- or -N(R^3)C(O)N(R^3)-;

(d) reacting a compound of Formula 2, or a protected derivative thereof, with an isocyanate of the formula R^1-NC(O), or a protected derivative thereof, and then deprotecting when necessary, to give a compound of Formula I in which X^2 is 1,4-piperazinylene or 1,4-piperidylene and X^1 is -NHC(O)- or in which X^2 is (C_{1-8})alkylene and X^1 is -NHC(O)N(R^3)-;

(e) reacting a compound of Formula 3:



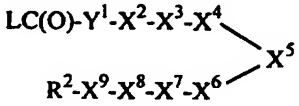
3

or a protected derivative thereof, with 2 or more molar equivalents of a compound of the formula R^1-Y^1-C(O)L, or a protected derivative thereof, wherein L is a leaving group, Y^1 is a bond, -O- or -N(R^3)-, Y^2 and Y^8 are independently piperazin-1-yl, piperid-4-yl or HN(R^3)-(C_{1-8})alkyl and each R^1, R^3, X^3, X^4, X^5, X^6 and X^7 are as defined in the Summary of the Invention, and then deprotecting when necessary, to give a compound of Formula I in which R^1 equals R^2; X^2 and/or X^8 is 1,4-piperazinylene or 1,4-piperidylene; X^1 is -C(O)-, -OC(O)- or -N(R^3)C(O)-; and X^9 is -C(O)-, -OC(O)- or -N(R^3)C(O)- and/or in which X^2 and/or X^8 is (C_{1-8})alkylene; X^1 is -C(O)N(R^3)-, -OC(O)N(R^3)- or -N(R^3)C(O)N(R^3)-; and X^9 -C(O)N(R^3)-, -OC(O)N(R^3)- or -N(R^3)C(O)N(R^3)-;

(f) reacting a compound of Formula 3, or a protected derivative thereof, with two or more molar equivalents of an isocyanate of the formula R^1-NC(O), or a protected derivative thereof, and then deprotecting when necessary, to give a compound of Formula I in which R^1 equals R^2;

X^2 and/or X^8 is 1,4-piperazinylene or 1,4-piperidylene; X^1 is -NHC(O)- and/or X^9 is -NHC(O)- and/or in which X^2 and/or X^8 is (C_{1-8})alkylene and X^1 is -NHC(O)N(R^3)- and/or X^9 is -NHC(O)N(R^3)-;

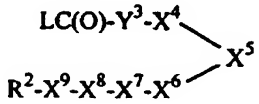
(g) reacting an amine of the formula R^1-N(R^3)H, or a protected derivative thereof, with a compound Formula 4:



4

or a protected derivative thereof, wherein L is a leaving group, Y^1 is a bond, -O- or -N(R^3)- and each R^1, R^2, R^3, X^2, X^3, X^4, X^5, X^6, X^7, X^8 and X^9 are as defined in the Summary of the Invention, and then deprotecting when necessary, to give a compound of Formula I in which X^1 is -N(R^3)C(O)-, -N(R^3)C(O)O- or -N(R^3)C(O)N(R^3)-;

(h) reacting a compound of the formula R^1-X^1-Y^2, or a protected derivative thereof, with a compound of Formula 5:

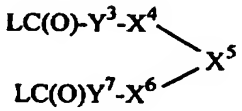


5

or a protected derivative thereof, wherein L is a leaving group, Y^3 is a bond, -O- or -N(R^3)-, Y^2 is piperazin-1-yl, piperid-4-yl or HN(R^3)-(C_{1-8})alkyl, respectively, and each R^1, R^2, R^3, X^1, X^2, X^3, X^4, X^5, X^6, X^7, X^8 and X^9 are as defined in the Summary of the Invention, and then deprotecting when necessary, to give a compound of Formula I in which X^2 is 1,4-piperazinylene or 4,1-piperidylene and X^3 is -C(O)-, -C(O)O- or -C(O)N(R^3)- or in which X^2 is (C_{1-8})alkylene and X^3 is -N(R^3)C(O)-, -N(R^3)C(O)O- or -N(R^3)C(O)N(R^3)-;

(i) reacting 2 or more molar equivalents of compound of the formula R^1-X^1-Y^2, or a

protected derivative thereof, with a compound of Formula 6:



6

or a protected derivative thereof, wherein L is a leaving group, Y^3 and Y^7 are independently a bond, -O- or -N(R^3)-, Y^2 is piperazin-1-yl, piperid-4-yl, HN(R^3)-(C_{1-8})alkyl or HN(R^3)-hetero(C_{1-8})alkyl and each R^1, X^1, X^4, X^5 and X^6 are as defined in the Summary of the Invention, and then deprotecting when necessary, to give a compound of Formula I in which X^2 and X^8 each are 1,4-piperazinylene or 4,1-piperidylene and X^3 and X^7 are independently -C(O)-, -C(O)O- or -C(O)N(R^3)- or in which X^2 and X^8 each are (C_{1-8})alkylene or hetero(C_{1-8})alkylene and X^3 and X^2 are independently -N(R^3)C(O)-, -N(R^3)C(O)O- or -N(R^3)C(O)N(R^3)-, respectively;

(j) optionally reacting a compound of Formula I in which R^4 is amino with cyanamide to give a compound of Formula I in which R^4 is guanidino;

(k) optionally further converting a compound of Formula I into a pharmaceutically acceptable salt;

(l) optionally further converting a salt form of a compound of Formula I to non-salt form;

(m) optionally further converting an unoxidized form of a compound of Formula I into a pharmaceutically acceptable *N*-oxide;

(n) optionally further an *N*-oxide form of a compound of Formula I its unoxidized form;

(o) optionally further converting a non-derivatized compound of Formula I into a pharmaceutically prodrug derivative; and

(p) optionally further converting a prodrug derivative of a compound of Formula I to its non-derivatized form.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 97/13422

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D295/20 C07D211/26 C07D233/14 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 845 242 A (JAMES C. POWERS) 4 July 1989 see column 1	14
A	WO 96 09297 A (ARRIS PHARMACEUTICAL CORPORATION) 28 March 1996 see page 0	14
A	WO 95 32945 A (ARRIS PHARMACEUTICAL CORPORATION) 7 December 1995 see page 0	14
A	WO 94 20527 A (ARRIS PHARMACEUTICAL CORPORATION) 15 September 1994 see page 46-63; claims	1-44

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

2

Date of the actual completion of the international search	Date of mailing of the international search report
26 November 1997	09. 12. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Luyten, H

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/13422

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 525 623 A (KERRY SPEAR ET AL) 11 June 1996 see the whole document	1-44
P,A	WO 96 30353 A (ARRIS PHARMACEUTICAL CORPORATION) 3 October 1996 see page 0	14
P,A	WO 96 40737 A (ARRIS PHARMACEUTICAL CORPORATION) 19 December 1996 see page 0	14

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 97/13422

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Remark : Although claims 15-22,36-43Remark : Although claims
are
directed to a method of treatment of the human/animal body , the search has been carried out and based on the alleged effects of the compound/composition.ed to a method of treatment of the human/animal body , the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 97/13422

Patent document cited in search report	Publication dat	Patent family member(s)	Publication date
US 4845242 A	04-07-89	US 4954519 A	04-09-90
		US 5089633 A	18-02-92
		US 5089634 A	18-02-92
		US 5324648 A	28-06-94
WO 9609297 A	28-03-96	AU 3718095 A	09-04-96
		CA 2200561 A	28-03-96
		EP 0782571 A	09-07-97
		FI 971171 A	20-03-97
		HR 950499 A	31-08-97
		LT 97065 A,B	25-08-97
		NO 971305 A	06-05-97
		PL 319587 A	18-08-97
		ZA 9508028 A	18-04-96
WO 9532945 A	07-12-95	AU 2764495 A	21-12-95
		EP 0763016 A	19-03-97
		US 5656660 A	12-08-97
WO 9420527 A	15-09-94	AU 683459 B	13-11-97
		AU 6364794 A	26-09-94
		CN 1119019 A	20-03-96
		CZ 9502321 A	17-07-96
		EP 0688337 A	27-12-95
		FI 954245 A	28-09-95
		JP 8507768 T	20-08-96
		NO 953522 A	07-09-95
		PL 310559 A	27-12-95
		SK 112995 A	01-10-96
		NZ 263084 A	22-08-97
		US 5525623 A	11-06-96
US 5525623 A	11-06-96	AU 683459 B	13-11-97
		AU 6364794 A	26-09-94
		CN 1119019 A	20-03-96
		CZ 9502321 A	17-07-96
		EP 0688337 A	27-12-95
		FI 954245 A	28-09-95
		JP 8507768 T	20-08-96
		NO 953522 A	07-09-95

INTERNATIONAL SEARCH REPORT

...formation on patent family members

International Application No
PCT/US 97/13422

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5525623 A		NZ 263084 A	22-08-97
		PL 310559 A	27-12-95
		SK 112995 A	01-10-96
		WO 9420527 A	15-09-94
WO 9630353 A	03-10-96	AU 5367496 A	16-10-96
		ZA 9602336 A	31-07-96
WO 9640737 A	19-12-96	AU 5975596 A	30-12-96

Form PCT/ISA/210 (patent family annex) (July 1992)